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# Ischaemic Heart Disease in Death Discordant Twins

A Study on 205 Male and Female Pairs

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STOCKHOLM 1974

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An increasing trend in the last decade has been noted by several authors (de Faire, 1966; Stamler, 1966; Sweden show a decrease in mortality (Blomquist, 1971)). The highest incidence is found in men (Blomquist, 1971). IHD is a leading cause of death and it has been shown that several factors are suspect (Atkinson, 1971). It is probable that at least one of these factors is as trying to preventive factors.

Prospective studies between the risk factors and statistically imply a causal relationship. Many examples have been published (Kannel, 1971; Epstein, 1971) from several studies seem to be atherosclerosis. When they have been identified lipoprotein levels, blood pressures, uricaemia and into biometric roots of may be susceptible.

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## INTRODUCTION

An increasing mortality from ischaemic heart disease (IHD) during the last decades, especially in men, has been reported by several authors (de Haas, 1964; Oliver & Stuart-Harris, 1965; Reader & Wynn, 1966; Stamler, 1973). However, figures from mortality statistics in Sweden show only a slight increase in men and a corresponding decrease in women (Biörck & Bylin, 1965; Biörck et al, 1970; Vedin et al, 1971). In comparisons between countries, male IHD mortality is highest in Finland and the USA, while Sweden comes comparatively low down (Blomqvist & Biörck, 1963; Moriyama et al, 1971).

IHD is no doubt a major international problem, causing early death and invalidity. The National Health Examination Survey has shown that several million persons in the USA have IHD, definite or suspect (Atherosclerosis Study Group, 1970). Thus it is understandable that great efforts are now concentrated on trying to prevent or at least delay the development of IHD (primary prevention) as well as trying to prevent relapses (secondary prevention). However, preventive action presupposes knowledge of the pertinent etiological factors.

Prospective population studies have demonstrated associations between the incidence of IHD and different variables, usually called risk factors. By risk factors are understood those factors which are statistically associated with IHD, but this does not necessarily imply a causal relationship.

Many extensive reviews concerning risk factors have been published (Kannel et al, 1961; Biörck, 1963; Keys & Blackburn, 1963; Epstein, 1967; Simborg, 1970; Fejfar, 1972; Stamler, 1973). Judging from several prospective studies, the major contributory factors seem to be hypertension, hypercholesterolaemia and smoking (Atherosclerosis Study Group, 1970). Their impact on risk is more pronounced when they are present in combination. Other risk factors have also been identified as for example hypertriglyceridaemia, various hyperlipoproteinaemias, overweight, sedentary living, psycho-social tensions, dietary factors, excessive alcohol consumption, hyperuricaemia and diabetes mellitus. The risk factors can be subdivided into biometric or intrinsic and environmental or extrinsic. The roots of many biometric factors are probably mostly genetic but they may be susceptible to the influence of environment. Similarly,

environmental factors may be linked in some measure to the genetic constitution (Björck, 1959).

The importance of the hereditary influence in IHD has always been stressed by Paul D. White (1957 and 1960). The general approaches to determining the strength and mechanism of genetic factors in chronic diseases have been described among others by Penrose (1953) and Edwards (1963). The methods available for observational study of the genetic basis of IHD have usually been the study of familial aggregation and twin studies.

#### Familial aggregation of ischaemic heart disease

Familial aggregation of IHD has often been accepted as an indication of a substantial genetic influence on IHD. Several studies have demonstrated such aggregation (Gertler & White, 1954; Thomas & Cohen, 1955; Russek & Zohmann, 1958; Shanoff et al, 1961; Rose, 1964). However, as pointed out by Mc. Kusick and Murphy (1963), modest familial concentrations have been found for most common diseases for which they have been sought. A contributory factor to the familial clustering of IHD found in retrospective studies could be that probands are more aware of relatives with the trait in question. In a report from the Tecumseh Community Health Study, Napier et al (1972) have shown that family history reports on morbidity are rather limited. The findings also suggested that mortality data obtained exclusively from family histories should be interpreted with great caution.

Prospective studies have also disclosed familial aggregation of IHD (Slack & Evans, 1966; Deutscher et al, 1970; Hammond et al, 1971). But according to Epstein (1964), the relative importance of familial influences in the genesis of IHD cannot be estimated quantitatively from the findings of family studies. It must be born in mind that the members of a family tend to share not only their genes but their environment.

#### Twin studies

Ever since the days of Galton (1822-1911), twins have been studied with regard to the genetic influence on chronic diseases. The possible contribution of twins in epidemiologic studies of chronic diseases was reviewed at a meeting in 1965 sponsored by WHO. It was stressed that twin studies offer a useful tool in evaluating the relative importance of heredity and environment for chronic conditions such as IHD. The methodology in twin studies has been carefully

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analysed by Cederlöf (1966) and others, including an international symposium in Puerto Rico in 1969. Several models have been suggested for testing specific hypotheses. The most common technique is probably the so called classical twin method, described by several authors (Dahlberg, 1926; von Verschuer, 1958; Gedda, 1961; Harvald & Hauge, 1965). Here the rate of concordance for some specific trait is compared between monozygotic (MZ) and dizygotic (DZ) twin pairs. A significantly higher degree of concordance in the MZ pairs speaks in favour of genetic factors being responsible for the difference. This conclusion assumes, however, that the intra-pair difference for MZ and DZ twins with respect to environmental factors is of about the same order, which may not be the case. Another assumption is an unbiased selection of pairs, but in practice there is often an over-representation of pairs with the trait under investigation.

A similar approach, used by Kaij (1960) and Cederlöf et al (1970), is to compare the observed and expected rates of coincidence. The observed rate is defined as the ratio between the number of pairs where both twins have the trait and the total number of pairs observed. The expected rate is calculated from the prevalence in the twin sample. The genetic dependence of continuous variables and the influence on them of environment are best studied by variance analysis (Osborne & de George, 1959; Takkenen, 1964). A less marked intra-pair difference in MZ pairs compared to DZ pairs indicates that the variable in question is more dependent on genetic than on environmental factors.

The co-twin control method, worked out by Gesell (1942), is especially suitable for studying the influence of specific environmental factors on health. It has the advantage of keeping the genetic factor under control. A typical example of this approach is the study of smoking discordant twins with respect to IHD and lung function (Lundman, 1966).

#### Ischaemic heart disease in twins

Several case reports have been published concerning concordance in MZ twin pairs (Parade & Lehmann, 1938; Froment et al, 1945; Bernasconi et al, 1957; Benedict, 1958; Giknis et al, 1965; Douglas, 1966; Sidd et al, 1966) but only a few concerning discordant pairs (Sulser & Koller, 1961; Lees et al, 1963). Although individual case reports on twin concordance for IHD obviously cannot prove the presence of heredity in IHD, they are sufficiently suggestive to raise a suspicion

of its presence. Kahler & Weber (1940) studied 17 twin pairs in which at least one of the twins suffered from IHD. Three of the four MZ pairs were concordant with respect to IHD, but only two of the DZ pairs. Reviewing several small twin materials, von Verschuer (1958) reported a combined IHD concordance of 19 % in the MZ pairs as compared to 8.5 % in the DZ pairs.

Only two representative, unselected twin samples, the Danish and the Swedish Twin Registries, are suitable for epidemiological studies.

The Danish Twin Registry was founded in 1954 and has been developed ever since (Harvald & Hauge, 1968). It contains information on medical and social conditions on about 8,000 unselected pairs of twins born in the period 1870 to 1910, where both partners had survived the age of five. By January 1, 1968, "coronary occlusion" had occurred in 352 twins. The rate of concordance has been calculated by the twin proband method (Allen et al, 1967), i.e. concordant pairs are counted twice, as both partners are considered probands. The concordance rate in the male MZ pairs, 39 %, differed significantly from that of 26 % in the male DZ pairs. In the female pairs the difference was much greater, 44 and 14 % respectively, giving significance at a higher level. The risk of a co-twin dying from "coronary occlusion" in the first 10 years after the proband's death was also calculated. For co-twins in MZ and DZ male pairs, the risk curves were very similar but for the female pairs they deviated considerably right from the start. The risk of a female MZ co-twin dying from "coronary occlusion" was over 40 % in the first 10 years after the proband's death as compared to about 4 % for a female DZ twin. The corresponding risks for the male MZ and DZ pairs were about 15 %. It was concluded that the occurrence of fatal "coronary occlusion" seemed to be genetically determined to a very limited extent in males, and to a much larger extent in females.

In a questionnaire study on the Swedish Twin Registry, Cederlöf et al (1967) evaluated the prevalence of angina pectoris, using the questions worked out by Rose (1962). The investigation comprised 2,255 MZ and 3,622 DZ twin pairs, 40 to 80 years of age, with concordant smoking habits. The results showed a significantly higher degree of coincidence of angina pectoris in MZ compared to DZ pairs for males as well as females in the age group 60-80 years, but for the younger age group 40-60 years, this was true only for the females. Validation of the mailed questionnaire concerning angina pectoris (Lundman et al, 1971) indicates that it is very useful for screening cases with IHD, but one has to be aware of a tendency to give false positives.

In a study of the Swedish Twin Registry, Liljefors (1968) found a significantly higher concordance of segmental electrocardiogram abnormalities in MZ compared to DZ pairs. It was suggested that the multiple dominant inheritance model included in the study was more prone to indicate a genetic effect in male and female twin conclusions. The non-smoking twin pairs were also included.

Liljefors (1968) found a significantly higher concordance in the Swedish Twin Registry for MZ compared to DZ pairs. The concordance was significantly higher for MZ than for DZ pairs of IHD was excluded. The use of electrocardiogram code and/or ST exercise) to identify twin pairs were compared. The difference was significant.

Although the results of the study were smaller than those of Liljefors et al (1968), these results were strong enough to suggest a genetic effect not to the same extent as in the Swedish Twin Registry.

#### Background and

The establishment of the Swedish Twin Registry for epidemiological studies of etiological factors in cardiovascular system. Environmental factors are also being studied. The investigation is carried out by the Serafimer Institute. The mortality follow-up study is also being carried out.

On In a study of 196 smoking discordant male and female twins from the Swedish Twin Registry, Lundman (1966) evaluated the occurrence of segmental ST depressions of at least 0.5 mm at post-exercise electrocardiography and found that the observed coincidence rate was significantly higher than the expected rate in both MZ and DZ pairs. It was suggested that these segmental changes could be due to multiple dominant genes. When the clinical picture of IHD was included in the judgement of IHD, the difference within the MZ pairs was more pronounced, but not within the DZ pairs, which was considered to indicate a substantial genetic component in IHD. However, female and male twin pairs were pooled in these analyses, obstructing further conclusions. The occurrence of IHD did not differ between smoking and non-smoking twin pairs.

ed Liljefors (1970) studied 91 male twin pairs, also from the Swedish Twin Registry, aged 42-67 years, who were concordant or discordant with respect to IHD. The concordance rate was calculated for different manifestations of IHD. For myocardial infarction, concordance was seen in one MZ pair and one DZ pair. When the concept of IHD was extended to include angina pectoris and/or pathological electrocardiographic findings ( $Q_2$  at rest according to the Minnesota code and/or ST segmental depressions of at least 0.5 mm during exercise) to indicate the probable presence of IHD, 48.5 % of the MZ pairs were concordant as compared to 28.5 % of the DZ pairs. The difference was, however, not statistically significant.

ly Although different manifestations of IHD have been measured, the results of these few twin studies do suggest some general comments. The differences found in concordance rates between MZ and DZ pairs were smaller in males than females (cf. Harvald & Hauge and Cederlöf et al). These findings could indicate that environmental factors are strong enough to outweigh or mask the genetic influences in men, but not to the same extent in women.

#### Background and objectives of the present study

The establishment of the Swedish Twin Registry provided a useful tool for epidemiological studies. It was set up primarily to study factors of etiologic importance for diseases of the respiratory and cardiovascular system. The Registry is administered by the Department of Environmental Hygiene, Karolinska Institute, and a research program is carried out in collaboration with the Department of Medicine at the Serafimer Hospital. One line of this program is a continuous mortality follow-up, another comprises clinical studies on subsamples

of the Twin Registry. At the international twin symposium in Puerto Rico in 1969 it was pointed out that no generally accepted methodology in the design of twin studies exists and there are many complex possibilities. Studies of mortality were considered of great importance and as valuable extensions, clinical examinations of the partners of deceased twins were suggested with a view to detecting any differences in disease prevalence between surviving MZ and DZ co-twins. No such studies have yet been carried out.

From January 1971, information on deceased twins has been available every month, thereby permitting clinical examination of the surviving co-twin reasonably soon after the death of the partner. This provided one of the pre-requisites for the present study. By using a sample of unselected death discordant twins, the surviving co-twins could be examined in an unbiased way with respect to various manifestations of IHD and risk factors. If an important genetic influence on IHD exists, it seems plausible that IHD, silent or manifest, will appear significantly more often in the most genetically predisposed twins, i.e. MZ co-twins whose partners have died from IHD as compared to DZ co-twins whose partners have died from IHD. The comparison should also be extended to the co-twins, whose partners have died from other causes than IHD, thus permitting a comparison between different genetically predisposed surviving co-twins. The objectives of the study can be summarized as follows:

- (1) Evaluate the genetic influence in IHD - is there an association between the occurrence of IHD in the surviving co-twin and the cause of death of the partner (IHD or not IHD)?
- (2) Is there an association between the risk factor profile in the surviving co-twin and the cause of death of the partner (IHD or not IHD)?
- (3) Are there environmental differences in the death discordant pairs as elucidated from earlier questionnaires?

Furthermore, this study provides a basis for a continuous follow-up of mortality of the co-twins examined and thus makes it possible to assess the predictive value of the measured risk factors as well as the hereditary influence.

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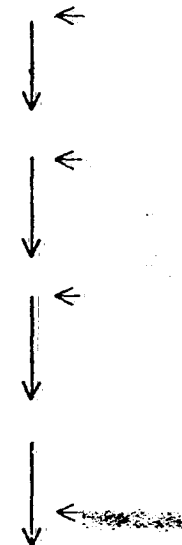


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# I MATERIAL

The material of death discordant twins for the present investigation derives from the Swedish Twin Registry and the study constitutes part of the research program for the Registry (Fig. 1).

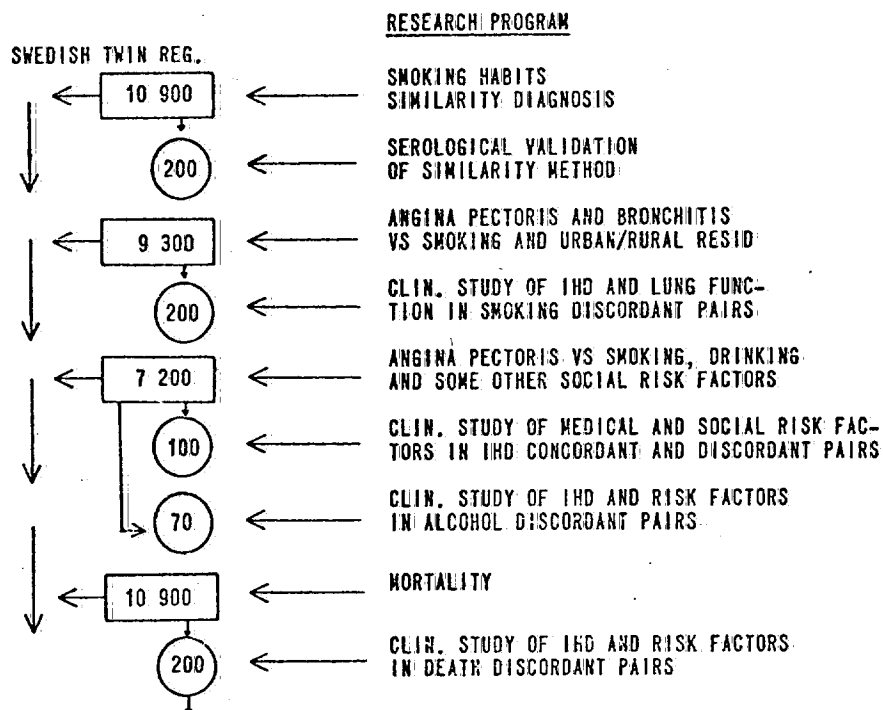


Fig. 1. Research program for the Swedish Twin Registry.

## The Swedish Twin Registry

The Swedish Twin Registry was set up in the years 1959 to 1961 at the departments of Environmental Hygiene, Karolinska Institute and the former National Institute of Public Health. It contains about 10,000 twin pairs and covers about 95 % of all Swedish same-sex twins who were born in the country between 1886 and 1925 and with both members living when the Registry was formed. The compilation procedure and the demographic structure of the twin series have been described in detail by Cederlöf (1966 a). The Registry has been used for several questionnaire studies, mainly dealing with respiratory symptoms and angina pectoris, with special reference to smoking (Cederlöf et al,

1966 b; Cederlöf et al, 1966 c; Cederlöf, 1966 d; Cederlöf et al, 1967 a; Cederlöf et al, 1967 b), and two clinical studies (Lundman, 1966; Liljefors, 1970).

#### Zygosity diagnosis

The zygosity of the twins in the Registry has been determined with the aid of similarity questions contained in a questionnaire, mailed to each one of them (Cederlöf, 1966 a). One of these items proved to be of high reliability, namely the very simple question, whether the twins as children were as alike as two peas in a pod, or of family likeness only. The questions were validated by Cederlöf et al (1961) on 200 randomly selected pairs by comparing the questionnaire diagnosis with blood-group serology in respect of five independent systems, namely A<sub>1</sub>A<sub>2</sub>BO, MN, Rh, Hp and Gm. The MZ and the DZ diagnosis arrived at from the questionnaire agreed with the serologic diagnosis in 99 % and 91 % respectively. About 4 % of the twins gave conflicting answers concerning similarity and have therefore been classified as of unknown zygosity (XZ). Excluding the XZ-group, the MZ twins make up 35.6 % of the men and 34.1 % of the women in the Registry. The zygosity diagnoses in the present study are exclusively based on the diagnoses earlier made in the Twin Registry.

#### Mortality evaluation

The mortality among the twins is established as follows. The total twin registry is matched regularly against a total death registry for Sweden at the Central Bureau of Statistics. Since 1971 this has been done once a month (Bolander, 1973). The procedure provides access to the death certificate and the name of the physician who signed it. The certificate in turn indicates whether or not the deceased twin had been treated in a hospital. Hospital records, autopsy records, information from general practitioners, and other pertinent information are collected. The cause of death is then established from all these records etc. The final evaluation has been made together with two other doctors (Drs. L. Friberg and T. Lundman) and the cause of death has been classified according to the 1965 revision of International Statistical Classification (ISC, 1969) of Diseases, Injuries, and Cause of Death, which has been used since 1969 in this country. Further details of the mortality evaluation will be found in two reports on the mortality follow-up in smoking discordant twins (Friberg et al, 1970 and 1973).

#### Criteria for

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Criteria for selection of the present material

During the period January 1st, 1971 to March 15th, 1973, 262 male and female twin pairs below the age of 70, became death discordant, i.e. one of the members in an unbroken pair died during the period mentioned above. About two or three months after death discordance had occurred, the surviving co-twins were invited to a thorough health check-up at Serafimer Hospital, Stockholm. The selection procedure is visualized in Fig. 2.

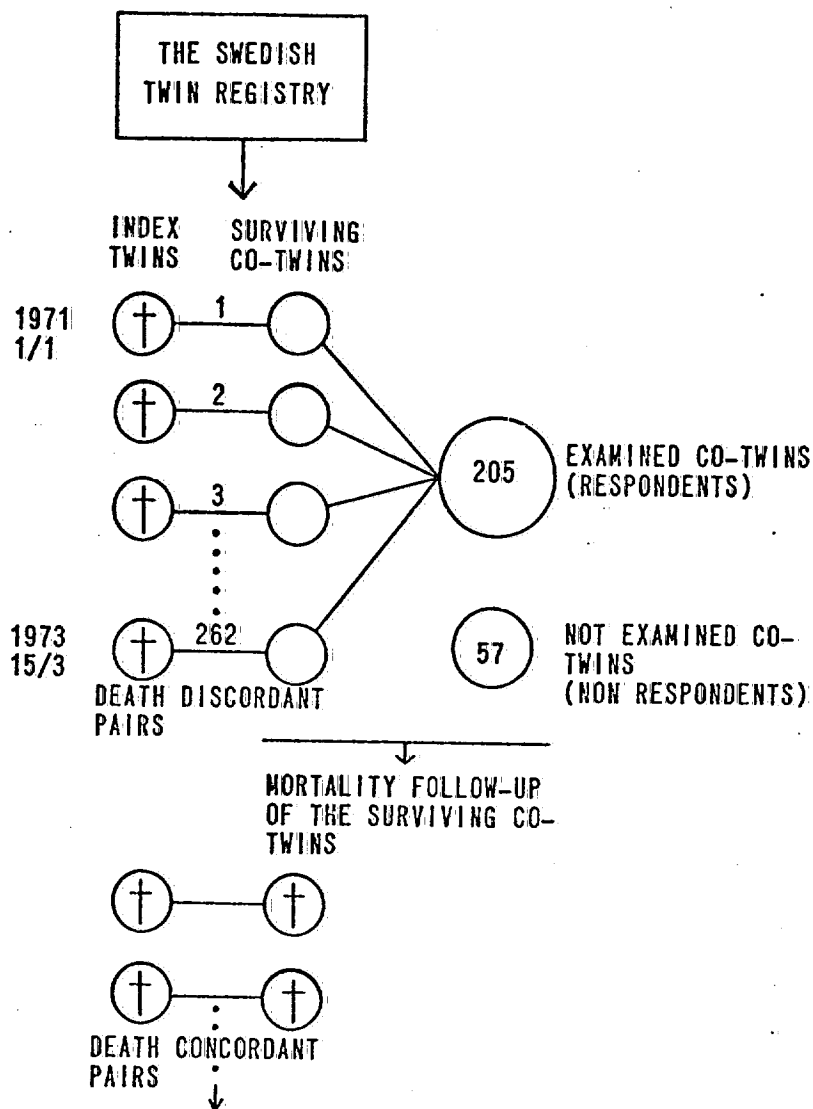


Fig. 2. Selection of the present material.

Table 1. Causes of death of the index-twins with a breakdown by sex.

	Males		Females		Both sexes	
	No.	%	No.	%	No.	%
All causes	141	100.0	121	100.0	262	100.0
IHD, total	48	34.0	21	17.4	69	26.3
Myocardial infarction	34	24.1	10	8.3	44	16.8
Other IHD			2	1.7	2	0.8
Sudden death	14	9.9	9	7.4	23	8.8
Not IHD, total	93	66.0	100	82.6	193	73.7
CVD	10	7.1	10	8.3	20	7.6
Malignant tumors	34	24.1	53	43.8	87	33.2
Uraemia	1	0.7	2	1.7	3	1.1
Diabetes mellitus	2	1.4	2	1.7	4	1.5
Suicides	8	5.7	4	3.3	12	4.6
Accidents	8	5.7	8	6.6	16	6.1
Other causes	30	21.3	21	17.4	51	19.5

#### The deceased twins

The deceased twins constitute the index-twins in the death-discordant pairs. A breakdown by cause of death, determined as earlier described, is given in Table 1, using the following groups (ISC numbers in parenthesis): IHD (410.00-414.99, 795.99), cerebrovascular diseases (CVD) (430.00-438.99), malignant tumors (140.01-209.99), uraemia (792.99), diabetes mellitus (250.00-250.09), suicides (E 950.9-E 959.9), accidents (800.00-999.99, E 807.0-E949.9, E 960.9-E 999.9), and other causes (conditions not specified here, but corresponding to the remaining ISC numbers). IHD here includes myocardial infarction (410.00-410.99), sudden death (795.99) and other IHD. The last heading contains only two female cases, both classified as 412.09 (arteriosclerosis cordis NUD, cum hypertonia). Those death discordant pairs whose index-twins have died from IHD are in the following referred to as I H D   d e a t h   d i s c o r d a n t. Correspondingly, those pairs whose index-twins died from other causes than IHD are referred to as n o t   I H D   d e a t h   d i s c o r d a n t.

Hospital records or similar sources of information were available in 224 out of the 262 deaths (85.5 %). For the remaining 38 deaths (14.5 %), only death certificates were available but additional information was sought in these cases from relatives and/or the surviving co-twin. An autopsy had been performed in 149 of the deceased twins, or 56.9 %. The cases referred to autopsy included 35 forensic post-mortems (13.4 %).

The IHD (69.6 %) occurred in 26.3 % of the twins. No exact information was obtained in 7 cases.

From the assessment of the medical history and the clinical history, the following diagnoses had been made:

- (1) Myocardial infarction
- (2) Angina pectoris

As autopsy was performed in 56.9 % of the cases, fresh or old changes (unstable angina, etc.) in the coronary arteries. There were either a pair or a single corresponding case. There were 7 (3.6 %).

#### The survivors

The first twin in the pair was the beginning of the study (the author of the study) of death not.

#### Respondent

The response rate of 262 twins was 78.2 %, but were with men and 3 women. Two of them were from Gothenburg, one from the Central County Hospital, and one from the County Hospital in Finspång.

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The IHD cases included 23 cases of sudden death, of which 16 (69.6 %) occurred within two hours after the onset of acute symptoms. No exact information was available about this interval in the other 7 cases.

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From the collected hospital records, autopsy protocols etc. an assessment was also made of whether the deceased twin had a preexisting history of IHD and/or autopsy findings indicating IHD. A preexisting history was considered most probable if one of the following two diagnoses had been present.

- 13.7  
1.6  
1.2  
1.1  
1.5  
4.6  
5.1  
19.5
- (1) Myocardial infarction, confirmed at hospital or evidence of old infarction in the resting ECG.
  - (2) Angina pectoris on effort.

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As autopsy findings indicating IHD were regarded the existence of fresh or old infarct of the myocardium and/or marked arteriosclerotic changes (uncuttable arteries and/or occlusions) of the coronary arteries. Thus, of the 23 cases of sudden death, 16 (69.6 %) had either a preexisting history of IHD or a positive autopsy. The corresponding figures for the 193 cases not assigned to the IHD group were 7 (3.6 %).

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The surviving co-twins

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The first twins were examined in June, 1971, and the last in the beginning of August, 1973. At the time of the check-up the investigator (the author in all cases) was aware neither of the index-twin's cause of death nor of the zygosity.

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Respondent co-twins

The response rates and causes of non-response are given in Table 2. Of 262 twins invited, 205 were examined, which gives a response rate of 78.2 %. Among those examined, 14 were unable to come to Stockholm but were willing to attend a hospital nearer their home. Of these, 3 men and 3 women were examined at Sahlgrenska Hospital in Gothenburg; two of them came from places in the County of Bohuslän, north of Gothenburg, the rest lived in Gothenburg. Another two men were examined at the Central County Hospital of Uddevalla and two women at the Central County Hospital of Lidköping. One woman and one man were examined at the County Hospital of Bollnäs, one man at the Central County Hospital of Karlstad and another man at the County Hospital of Finspång.

Table 2. Response rates and causes of non-response by sex and zygosity.

	MZ		DZ		XZ		Tot.	
	No.	%	No.	%	No.	%	No.	%
<b>Males:</b>								
Total in sample	41	100.0	94	100.0	6	100.0	141	100.0
Total examined	35	85.4	67	71.3	6	100.0	108	76.6
Examined in Stockholm	34	82.9	61	64.9	5	83.3	100	70.9
Examined in the provinces	1	2.4	6	6.4	1	16.7	8	5.7
Not examined: total	6	14.6	27	28.7	0	0.0	33	23.4
No contact	1	2.9	2	2.1	0	0.0	3	2.1
Illness	2	4.9	7	7.4	0	0.0	9	6.4
Refusals owing to work	1	2.4	7	7.4	0	0.0	8	5.7
Refusals for other reasons	2	4.9	8	8.5	0	0.0	10	7.1
Data losses	0	0.0	3	3.2	0	0.0	3	2.1
<b>Females:</b>								
Total in sample	47	100.0	72	100.0	2	100.0	121	100.0
Total examined	38	80.9	57	79.2	2	100.0	97	80.2
Examined in Stockholm	35	74.5	54	75.0	2	100.0	91	75.2
Examined in the provinces	3	6.4	3	4.2	0	0.0	6	5.0
Not examined: total	9	19.1	15	20.8	0	0.0	24	19.8
No contact	2	4.3	0	0.0	0	0.0	2	1.7
Illness	3	6.4	2	2.8	0	0.0	5	4.1
Refusals owing to work	1	2.1	2	2.8	0	0.0	3	2.5
Refusals for other reasons	2	4.3	10	13.9	0	0.0	12	9.9
Data losses	1	2.1	1	1.4	0	0.0	2	1.7
<b>Both sexes:</b>								
Total in sample	88	100.0	166	100.0	8	100.0	262	100.0
Total examined	73	83.0	124	74.7	8	100.0	205	78.2
Examined in Stockholm	69	78.4	115	69.3	7	87.5	191	72.9
Examined in the provinces	4	4.5	9	5.4	1	12.5	14	5.3
Not examined: total	15	17.0	42	25.3	0	0.0	57	21.8
No contact	3	3.4	2	1.2	0	0.0	5	1.9
Illness	5	5.7	9	5.4	0	0.0	14	5.3
Refusals owing to work	2	2.3	9	5.4	0	0.0	11	4.2
Refusals for other reasons	4	4.5	18	10.8	0	0.0	22	8.4
Data losses	1	1.1	4	2.4	0	0.0	5	1.9

Table 3. Distribution of respondent co-twins (by sex and zygosity) according to cause of death of index-twin.

	NUMBER OF RESPONDENT CO-TWINS											
	Males				Females				Both sexes			
	MZ	DZ	XZ	Tot.	MZ	DZ	XZ	Tot.	MZ	DZ	XZ	Tot.
All causes	35	67	6	108	38	57	2	97	73	124	8	205
IHD, total	10	25	5	40	8	9	0	17	18	34	5	57
Myocardial infarction	8	18	4	30	3	5	0	8	11	23	4	38

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usa	or	ns	4	4.2	4	2.4	0	0.0	5	1.9
Data losses			1	1.1						

Table 3. Distribution of respondent co-twins (by sex and zygosity) according to cause of death of index-twin.

	NUMBER OF RESPONDENT CO-TWINS											
	Males				Females				Both sexes			
	MZ	DZ	XZ	Tot.	MZ	DZ	XZ	Tot.	MZ	DZ	XZ	Tot.
All causes	35	67	6	108	38	57	2	97	73	124	8	205
IHD, total	10	25	5	40	8	9	0	17	18	34	5	57
Myocardial infarction	8	18	4	30	3	5	0	8	11	23	4	38
Other IHD	0	0	0	0	1	1	0	2	1	1	0	2
Sudden death	2	7	1	10	4	3	0	7	6	10	1	17
Not IHD, total	25	42	1	68	30	48	2	80	55	90	3	148
CVD	2	4	0	6	2	5	0	7	4	9	0	13
Malignant tumors	9	18	0	27	19	21	2	42	28	39	2	69
Uraemia	1	0	0	1	0	2	0	2	1	2	0	3
Diabetes mellitus	0	1	0	1	0	1	0	1	0	2	0	2
Suicides	2	3	0	5	1	2	0	3	3	5	0	8
Accidents	1	6	0	7	1	5	0	6	2	11	0	13
Other causes	10	10	1	21	7	12	0	19	17	22	1	40

Table 4. Distribution of mean ages (years) of respondent co-twins (by sex and zygosity) according to cause of death of index twin.

	Males				Females				Both sexes			
	MZ	DZ	XZ	Tot.	MZ	DZ	XZ	Tot.	MZ	DZ	XZ	Tot.
	M (SE)	M (SE)	M (SE)	M (SE)	M (SE)	M (SE)	M (SE)	M (SE)	M (SE)	M (SE)	M (SE)	M (SE)
All causes	61.1 (1.1)	60.4 (0.8)	58.0 (3.2)	60.5 (0.6)	59.7 (1.1)	61.5 (0.8)	60.5 (1.5)	60.8 (0.6)	60.4 (0.8)	60.9 (0.5)	58.6 (2.4)	60.7 (0.4)
IHD, total	57.7 (1.8)	63.0 (0.8)	57.2 (3.8)	60.9 (0.9)	63.3 (2.2)	64.9 (1.8)	0	64.1 (1.4)	60.2 (1.5)	63.5 (0.8)	57.2 (3.8)	61.9 (0.8)
Myocardial infarction	59.0 (1.9)	63.7 (1.0)	59.5 (4.0)	61.9 (1.0)	57.7 (4.2)	62.6 (2.9)	0	60.8 (2.4)	58.6 (1.7)	63.5 (0.9)	59.5 (4.0)	61.7 (0.9)
Other IHD	0	0	0	0	65.0 (0.0)	69.0 (0.0)	0	67.0 (2.0)	65.0 (0.0)	69.0 (0.0)	0	67.0 (2.0)
Sudden death	52.5 (3.5)	61.0 (1.3)	48.0 (0.0)	58.0 (1.9)	67.0 (1.2)	67.3 (0.9)	0	67.1 (0.7)	62.2 (3.3)	62.9 (1.3)	48.0 (0.0)	61.8 (1.6)
Not IHD, total	62.5 (1.3)	59.0 (1.1)	62.0 (0.0)	60.3 (0.8)	58.8 (1.2)	60.9 (0.8)	60.5 (1.5)	60.1 (0.7)	60.5 (0.9)	60.0 (0.7)	61.0 (1.0)	60.2 (0.5)

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The distribution of the places of residence of the respondent co-twins is shown in Fig. 3. The places of residence are scattered over most of Sweden and seem to correspond fairly well with the population density.

In Table 3 the examined co-twins are distributed according to the cause of death of the index-twin. There were 57 (27.8 %) whose partners had died from IHD, i.e. 40 of the 108 male pairs (37.0 %) and 17 of the 97 female pairs (17.5 %). Sudden death caused 25 % of the IHD deaths among the males and 41.2 % among the females. It is also worth noting that of the 8 pairs of unknown zygosity (XZ), as many as 5 were male IHD death discordant.



Fig. 3. Distribution of the places of residence of the respondent co-twins. The figures in the two circles indicate the number of co-twins living in Stockholm and Gothenburg.

The distribution of the respondent co-twins by 5-year age groups is shown in Fig. 4, and Table 4 gives the means for age by the cause of death of the index-twin.

The mean age at the time of death discordance for all the respondent co-twins was 60.7 years. Among the IHD death discordant pairs, the mean age of the male MZ pairs, 57.7 years, was on average 5.3 years lower than that of the corresponding DZ pairs. The male MZ twins whose index-twins had died from causes other than IHD had a mean age of 62.5 years compared with 59.0 years for the corresponding DZ pairs. The mean ages of the male XZ pairs in the different death discordant groups are about the same as for the male MZ pairs. Among the female IHD death discordant pairs, the mean ages for both the MZ pairs and the DZ pairs, 63.3 years and 64.9 years respectively, are 4.5 and 4.0 years higher than for the MZ and DZ pairs whose index-twins died from other causes than IHD.

The surviving co-twins were examined on average about 5 months after the death of the index-twin (Table 5), the interval ranging between two and 12 months.

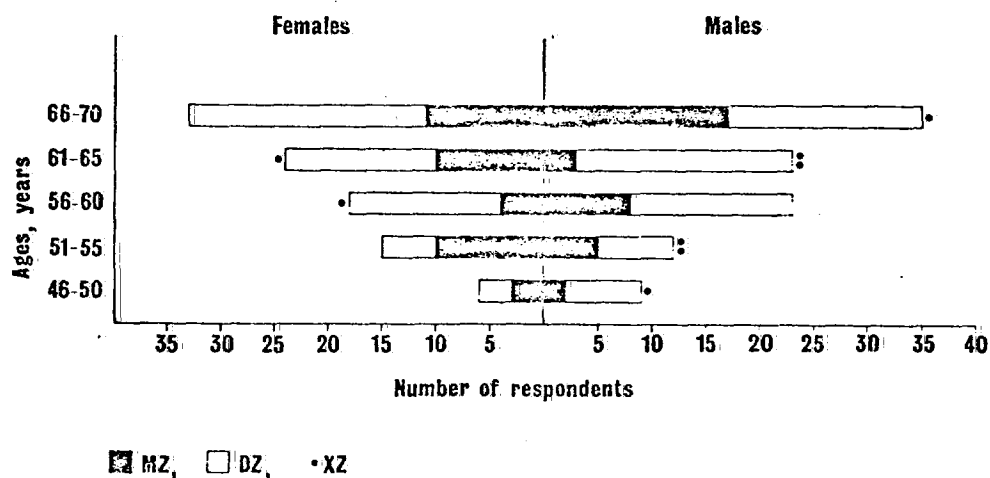


Fig. 4. Distribution of respondent co-twins by 5-year age groups.

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Table 5. Distribution of interval (mean and range in months) between death of index-twin and examination of co-twin according to cause of death of index-twin.

Cause of death of the index-twin	MZ		DZ		XZ		Tot.	
	M	Range	M	Range	M	Range	M	Range
Males	IHD	n=10 4.9 4.0-6.0	n=25 5.5 2.5-12.0	n=5 4.0 3.0-6.0	n=40 5.2 2.5-12.0			
	not IHD	n=25 5.6 3.0-12.0	n=42 5.3 2.0-11.0	n=1 9.0	n=68 5.5 2.0-12.0			
Females	IHD	n= 8 5.3 3.0-9.0	n= 9 5.6 3.0-10.0	n=0	n=17 5.4 3.0-10.0			
	not IHD	n=30 4.8 2.0-8.0	n=48 5.0 2.0-11.0	n=2 5.3 5.0-5.5	n=80 5.0 2.0-11.0			
Both sexes	IHD	n=18 5.1 3.0-9.0	n=34 5.5 2.5-12.0	n=5 4.0 3.0-6.0	n=57 5.2 2.5-12.0			
	not IHD	n=55 5.2 2.0-12.0	n=90 5.2 2.0-11.0	n=3 6.5 5.0-9.0	n=148 5.2 2.0-12.0			

#### Non-respondent co-twins

There were 57 twins who did not participate in the study (Table 2). Of these, 5 could not be traced in spite of attempts by letter and telephone. Another 14 were unable to participate owing to illness. Two of them, both men, were patients at mental hospitals, while two other men were patients at long-term clinics. One of the latter (MZ) died, however, in Morbus Alzheimer only 7 months after the index-twin. The cause of death attributed to the index-twin was cerebro-vascular disease. One female and one male twin were unable to participate because of invalidity after cerebral haemorrhage; the male twin (DZ) died from a myocardial infarction about 8 months after the death of the index-twin, which had been caused by cancer of the stomach. Another male twin (DZ) could not attend the examination because of general fatigue and weakness. He died later from a bronchopneumonia about 16 months after the index-twin, for whom the cause was cancer of the prostate gland. An unspecified neurological disorder made participation impossible for another male twin. Two twins were tied to wheel-chairs, one woman because of invalidity after poliomyelitis and one man because of a marked general rheumatoid arthritis. One

female and one male twin had recently been operated for gallbladder disease and cerebral malignant tumor respectively. Finally one woman was convalescent after a fracture of the femur and another was unable to participate because of general fatigue; she also suffered from hypertension.

Lack of time on account of work was the reason given by 11 twins, 8 male and 3 female, for refusing to participate. They were all offered an examination at their home hospital. Among the other refusals were 6 twins who declared a negative attitude towards health check-ups in general. The remaining 16 twins in this group supplied no definite reason for not participating.

As already mentioned, the total Twin Registry is matched regularly with a total death registry for Sweden; since 1971 this is done every month. The procedure involves a slight risk of incorrect matching. Because of this, the Twin Registry has been matched twice so far with the total registry of living people in the country. The first time was in January 1971 and the second in September 1973. At the last check, which covered the time of the present investigation, it was found that 5 of the twins had been incorrectly matched. They are listed in the table as data losses.

A breakdown of the non-respondent co-twins by the cause of death of the index-twins is given in Table 6. There were 12 non-responders (21.1 %) whose partners had died from IHD, which is a somewhat lower proportion compared to the respondent group; this is especially true for the males. It will also be seen that there are no XZ pairs among the non-respondents. Furthermore, the percentage of MZ (the XZ omitted) among the males is less than for the respondents, 18.2 and 34.3 respectively. Among the females there are no substantial differences of this kind.

Figure 5 shows the distribution of the non-responders by 5-year age groups and Table 7 the means for age by the cause of death of the index-twin.

The mean age of the male IHD death discordant pairs, 61.3 years, is only 0.4 years higher than the mean for the corresponding group of respondent males. However, the non-responding male co-twins (only DZ pairs) whose index-twin died from myocardial infarction are on average 7.4 years younger than the corresponding male DZ twins among the responders, 56.3 years and 63.7 years respectively. The opposite age trend is seen in the non-responding male co-twins whose index-twin died from sudden death (MZ + DZ pairs), the mean age, 66.3 years, being on average 8.3 years higher than that of the corresponding respondents.

Table 6. Distribution of non-respondent co-twins (by sex and zygosity) according to cause of death of index-twin.

NUMBER OF NON-RESPONDENT CO-TWINS						Both sexes		
Males			Females			MZ	DZ	XZ
MZ	DZ	XZ	MZ	DZ	XZ	Tot.	Tot.	Tot.

Table 6. Distribution of non-respondent co-twins (by sex and zygosity) according to cause of death of index-twin.

	NUMBER OF NON-RESPONDENT CO-TWINS											
	Males				Females				Both sexes			
	MZ	DZ	XZ	Tot.	MZ	DZ	XZ	Tot.	MZ	DZ	XZ	Tot.
All causes	6	27	0	33	9	15	0	24	15	42	0	57
IHD, total	1	7	0	8	2	2	0	4	3	9	0	12
Myocardial infarction	0	4	0	4	1	1	0	2	1	5	0	6
Other IHD	0	0	0	0	0	0	0	0	0	0	0	0
Sudden death	1	3	0	4	1	1	0	2	2	4	0	6
Not IHD, total	5	20	0	25	7	13	0	20	12	33	0	45
CVD	2	2	0	4	1	2	0	3	3	4	0	7
Malignant tumors	2	5	0	7	3	8	0	11	5	13	0	18
Uraemia	0	0	0	0	0	0	0	0	0	0	0	0
Diabetes mellitus	0	1	0	1	0	1	0	1	0	2	0	2
Suicides	0	3	0	3	1	0	0	1	1	3	0	4
Accidents	0	1	0	1	1	1	0	2	1	2	0	3
Other causes	1	8	0	9	1	1	0	2	2	9	0	11

Table 7. Distribution of mean ages (years) of non-respondent co-twins (by sex and zygosity) according to cause of death of index twin.

	Males				Females				Both sexes			
	MZ	DZ	XZ	Tot.	MZ	DZ	XZ	Tot.	MZ	DZ	XZ	Tot.
	M (SE)	M (SE)	M (SE)	M (SE)	M (SE)	M (SE)	M (SE)	M (SE)	M (SE)	M (SE)	M (SE)	M (SE)
All causes	64.5 (1.2)	60.8 (1.3)	0	61.5 (1.1)	59.3 (2.1)	61.6 (1.5)	0	60.8 (1.2)	61.4 (1.5)	61.1 (1.0)	0	61.2 (0.8)
IHD, total	62.0 (0.0)	61.1 (2.7)	0	61.3 (2.3)	62.5 (4.5)	53.5 (4.5)	0	58.0 (3.7)	62.3 (2.6)	59.4 (2.4)	0	60.2 (1.9)
Myocardial infarction	0	56.3 (2.4)	0	56.3 (2.4)	58.0 (0.0)	49.0 (0.0)	0	53.5 (4.5)	58.0 (0.0)	54.8 (2.4)	0	55.3 (2.0)
Other IHD	0	0	0	0	0	0	0	0	0	0	0	0
Sudden death	62.0 (0.0)	67.7 (0.9)	0	66.3 (1.5)	67.0 (0.0)	58.0 (0.0)	0	62.5 (4.5)	64.5 (2.5)	65.3 (2.5)	0	65.0 (1.7)
Not IHD, total	65.0 (1.3)	60.6 (1.5)	0	61.5 (1.3)	58.4 (2.5)	62.8 (1.3)	0	61.3 (1.3)	61.2 (1.8)	61.5 (1.1)	0	61.4 (0.9)

Ages, years

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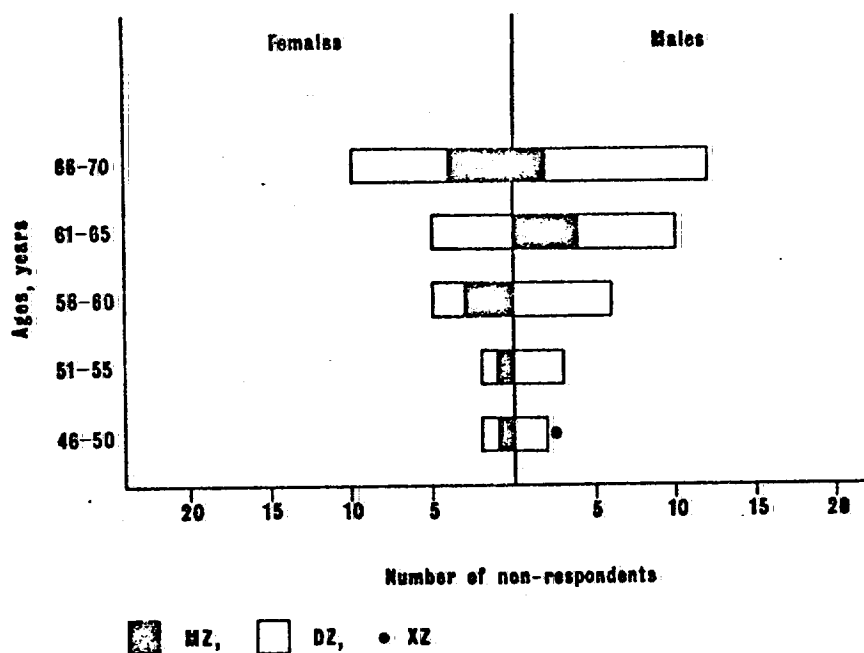


Fig. 5. Distribution of non-respondents by 5-year age groups.

#### Comments

One of our best measures of the reliability of mortality statistics is probably a high autopsy rate (Britton, 1974). In 1968 the autopsy rate in Sweden was about 45 % of all deaths, while for the age span 1-64 years it amounted to about 50 % (Vedin et al, 1971), which corresponds fairly well with the figure of about 57 % in the present material. For accurate mortality evaluation, however, an autopsy rate of 57 % seems rather low. This is unfortunately a problem for all kinds of mortality follow-ups which include people living outside the university cities in Sweden.

The death of the index-twins has been classified in 23 cases as sudden and unexpected and been included in the IHD group. The definition of sudden death varies considerably. An international committee has agreed upon a definition to facilitate international comparisons, sudden death being defined as death occurring immediately or within an estimated period of 24 hours after the onset of acute objective and subjective symptoms (Paul & Schatz, 1971). Other time criteria are also commonly used, e.g. one hour (Chiang et al, 1969 and 1970; Gordon & Kannel, 1971) or two hours (Adelson L., 1961; Kuller et al. 1966). In a study of 967 medically unattended deaths from IHD occurring

in Stockholm during one year (Wikland, 1971), information concerning the time relationship between the onset of symptoms of the fatal attack and death was obtained in 62 %. Of these, 61 % of the male and 48 % of the female cases died within 15 minutes of onset of symptoms. The definitions of sudden death have been carefully analysed in an editorial in *Circulation* (Björck & Wikland, 1972). It was pointed out that the accuracy of a statement of sudden death usually depends on the observer and from that point of view, it is important to note whether the preceding attack was witnessed or not (by any observer). It was furthermore concluded that for unwitnessed deaths it is difficult to know how "sudden" death occurred but a comparable proportion of these cases can usually be estimated to have occurred within the same time intervals as the witnessed ones.

About 70 % of the sudden deaths in the present investigation occurred within two hours and were witnessed. 30 % were unwitnessed and occurred without exact information of time but probably within 24 hours. The persons who died suddenly in hospital with signs of acute myocardial damage on the ECG or at autopsy have been classified not as sudden death but as myocardial infarction. Nor were those persons included among the sudden deaths, who died suddenly but with strong indications of other probable explanations for the cause of death. It is well known that, especially with the 24 hour interval, other causes than IHD may have been responsible for death, as for instance major sudden cerebrovascular hemorrhage, pulmonary embolism, asthma bronchiale and rheumatic heart diseases, especially aortic stenosis (Kuller, 1966; Moberg, 1969; Wikland, 1971; Vedin et al, 1973).

Of the 23 index-twins classified as sudden deaths, 16 (69.6 %) had either a preexisting history of IHD or autopsy findings indicating the presence of IHD. Of these 16, 11 were among the 16 (68.7 %) who died within two hours and 5 were among the 7 (71.4 %) who died within 24 hours. In the 7 of the 23 (30.4 %) without earlier evidence of IHD, it seemed reasonable to suppose, however, that the sudden death was most probably the initial clinical manifestation of previously unknown IHD. This is in accordance with earlier reports, which point to incidences of about 20-25 % (Kuller et al, 1966; Kuller, 1966).

One of the problems in epidemiological studies is the lack of complete participation. This difficulty is of course more pronounced if the population under study is drawn from the whole of Sweden instead of a more restricted area. The present response rate of 78.2 % can be compared with a rate of 79.4 % in a co-twin control study of 196 smoking discordant twins by Lundman (1966) and 87.5 % response in

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a study of IHD in 91 twin pairs by Liljefors (1970). In the two latter studies there were some geographical restrictions with respect to the residence of the twin pairs. Lundman took his twin sample from several towns in the central parts of Sweden and Liljefors obtained his DZ pairs from 10 counties in central Sweden. There were no such restrictions in the selection of twin pairs in the present study. Furthermore, the mean age of the present twins was 60.7 years, which is about 3 years higher than in Liljefors' study and about 10 years higher than in Lundman's, a circumstance which might also tend to lower the response rate.

In population studies concerned with a particular disease it has been recognized that persons with the disease in question are more likely to participate than others (Cobb et al, 1957). The twin pairs in the present investigation were accordingly not informed that the primary intention was to study IHD. They were told that this was a general health check-up, constituting part of the research program on the Swedish Twin Registry and furthermore that only the surviving co-twins in death discordant pairs were included.

A non-participation group is often thought to differ in various ways from the group examined. In a population study of 973 50-year-old men (Tibblin, 1967), an analysis of the non-participants (Tibblin, 1965) failed to show that they were more sick than those examined. It was also found that the chief reason for non-participation (38 %) was a negative attitude to medical care in general. In the present investigation, the largest group of non-response (22 out of 57) has been labelled "refusals for other reasons". This includes 6 persons who frankly declared a negative attitude to doctors, hospitals and health check-ups. The rest of this group (16 persons) gave no reason for their refusal.

As regards age, sex and zygosity, there are some differences between the respondents and non-respondents. The male MZ twins clearly show a greater willingness to participate than the DZ males and this readiness seems to be independent of the partner's cause of death. There is no such difference among the female twins. The male twins who did not participate were also on average one year older than the respondents. It is of course difficult, not to say impossible, to tell whether the observed differences can influence a valid comparison between the zygosity groups. However, the prevalence of IHD as estimated from an earlier questionnaire did not reveal any substantial differences between the respondents and non-respondents.

## II METHODS

### Time schedule for the examinations

The first co-twins to be examined were seen in June 1971 and the last 26 months later, in August 1973.

The twins arrived at about 8.00 a.m. for the examination, which was completed by 4.00 p.m. on the same day. One or two twins a day were examined. The procedures were undertaken according to a fixed time schedule.

### Questionnaire and interviews

The twins were all interviewed by the author in accordance with special questionnaires, including questions on earlier diseases, hospital treatment and medication as well as questions on sociologic data, smoking habits, use of alcoholic beverages. The questions on cardiovascular symptoms followed a questionnaire designed at the London School of Hygiene and Tropical Medicine (Rose, 1962). The questionnaire on respiratory symptoms was based on that worked out by the British Medical Research Council (1960).

### Physical examination

A routine clinical bedside examination was performed on every twin, supplemented with the following examinations.

### Blood pressure measurements

The blood pressure was measured in supine position by the author, once at the beginning of the examination (casual blood pressure) and then after at least 15 minutes rest (basal blood pressure). A mercury manometer was used, with a sleeve measuring 13 x 40 cm, and the standard procedure recommended by WHO (1968) was followed. The blood pressure was read to the nearest 5 mm Hg. The systolic pressure level was determined by the first perception of sound. The diastolic fourth-phase level was recorded when the sounds were fully muffled and the diastolic fifth-phase when the sounds disappeared.

### Anthropometric measurements

Weight was measured to the nearest kilogramme with the subject

dressed in under

Height was measured barefooted and

Skinfold thickness was measured with a caliper (Edward) at subscapular and triceps measurements were taken to the nearest

Relative height index, calculated as

Arm circumference was measured in centimetre at

### Electrocardiography

ECGs were recorded during and after exercise and with CR<sub>2</sub>, CR<sub>4</sub>, CR<sub>5</sub> and bicycle, registered each load with (1961). The exercise was performed at 100 meter/min. (kpm) stepwise after 100 kpm/min. and for exercise, ECGs were recorded in leads: I,

A direct writing ECG was recorded on subjects examined at Solna, Sweden) with a direct writing ECG machine (Schönander AB, Stockholm) (Monark-Crescendo). All the subjects were examined dynamically before and after the exercise load. The ECG was recorded with a paper speed of 25 mm/sec. the ECG.

dressed in undershorts.

H e i g h t was measured to the nearest centimetre with the subject barefooted and his back against the wall.

S k i n f o l d t h i c k n e s s was measured with a Harpenden caliper (Edwards et al, 1955) giving a pressure of  $10 \text{ g/mm}^2$  in the subscapular and triceps areas on the right side of the body. Two measurements were performed at each site and the mean was recorded to the nearest 0.2 mm.

R e l a t i v e w e i g h t was determined according to a weight/height index,  $\frac{\text{weight (kg)}}{\text{height (cm)}^2} \times 100$ .

A r m c i r c u m f e r e n c e was measured to the nearest 0.5 centimetre at the mid of the pendant, unclothed right upper arm.

#### Electrocardiographic examination

ECGs were recorded at rest and, for nearly all of the subjects, also during and after an exercise test on a bicycle ergometer. The recordings were made after about 10 minutes' rest in supine position before exercise and with the following leads: I, II, III, aVR, aVL, aVF, CR<sub>1</sub>, CR<sub>2</sub>, CR<sub>4</sub>, CR<sub>5</sub> and CR<sub>7</sub>. During exercise with the subject sitting on a bicycle, registrations were performed after 2, 4, 5 and 6 minutes at each load with the leads CH<sub>2</sub>, CH<sub>4</sub>, CH<sub>5</sub> and CH<sub>7</sub> (Holmgren & Strandell, 1961). The exercise test started generally at a load of 300 kilopond-meter/min. (kpm/min.) for both men and women. The load was increased stepwise after the completion of each 6-min. period, for men by 300 kpm/min. and for women by 150 kpm/min. 1, 3 and 10 minutes after exercise, ECGs were again recorded in supine position with the following leads: I, II, III, CR<sub>1</sub>, CR<sub>2</sub>, CR<sub>4</sub>, CR<sub>5</sub>, CR<sub>7</sub>.

A direct writing 4-channel electrocardiograph was used on the subjects examined in Stockholm (Mingograph 42, Elema-Schönander AB, Solna, Sweden); those in the provinces were mostly examined with a direct writing 6 channel electrocardiograph (Mingograph 61, Elema-Schönander AB, Solna, Sweden). A mechanically braked bicycle ergometer (Monark-Crescentbolagen AB, Stockholm, Sweden) was used, the same for all the subjects but one, examined in Karlstad, where an electro-dynamically braked bicycle ergometer was used (Elema-Schönander, Solna, Sweden). The paper speed for the registrations was 50 mm/sec. before and after the test and also during the 5-min. registrations at each exercise load. The other recordings during exercise were performed with a paper speed of 25 mm/sec. The heart rate was calculated from the ECG.

The test was stopped when the patient was unable to continue due to fatigue, dyspnoea, angina pectoris or marked ST segment depression or serious arrhythmia. In some cases the test was discontinued earlier for orthopaedic reasons.

**Working capacity.** The maximum working capacity ( $W_{max}$ ) was calculated according to a formula of Strandell (1964). To the greatest load the subject was able to perform for 6 minutes ( $W_6$ ) was added  $n \times W_d/6$  kpm/min., where  $n$  is the number of minutes at the final load and  $W_d$  the difference between the two highest loads.

**Coding.** The ECGs were all coded by the author according to a modified system (Åstrand et al, 1967) of the original Minnesota Code (Blackburn et al, 1960).

The codings were made by the author over a period of about one month after completion of the study. All the ECGs were checked twice and some were also interpreted by an independent observer (Dr. T. Lundman).

#### Radiologic examination

Radiologic examination of heart and lungs was performed on every subject. The exposures were taken with the subject erect and in two planes (frontal and lateral). The tube-film distance for both positions was 1.5 m at all examinations. An experienced radiologist (Dr. G. Skogsberg) examined all the films and determined the total and relative heart volume (Jonzell, 1939).

#### Blood investigations

At about 8.00 a.m. venous blood samples were drawn after about 12 hours fast and thirst. All the analyses on blood from the subjects examined in Stockholm were made at the Department of Clinical Chemistry, Serafimer Hospital. In the case of subjects examined outside Stockholm serum was obtained and transported in thermoses with carbonic acid snow, for later analysis of cholesterol triglycerides, and uric acid at the Department of Clinical Chemistry, Serafimer Hospital.

**Cholesterol** was determined in an autoanalyzer according to the modified method of Levine & Zak (1964).

**Triglycerides** were determined in an autoanalyzer by the method of Noble & Campbell (1970).

**Uric acid** was determined in an autoanalyzer by the method of Hawk et al (1954).

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Fig. 6. S  
co-twins.

The methods were checked continuously throughout the study by determinations on standard serum.

The other blood tests included fasting blood sugar, hemoglobin, venous hematocrit, erythrocyte sedimentation rate (E.S.R.) as well as qualitative tests for urine protein and urine glucose. The determinations were made at the hospital in question in accordance with the routine methods used there.

#### Statistical methods

Continuous and discrete variables among the surviving co-twins were compared according to the scheme in Fig. 6.

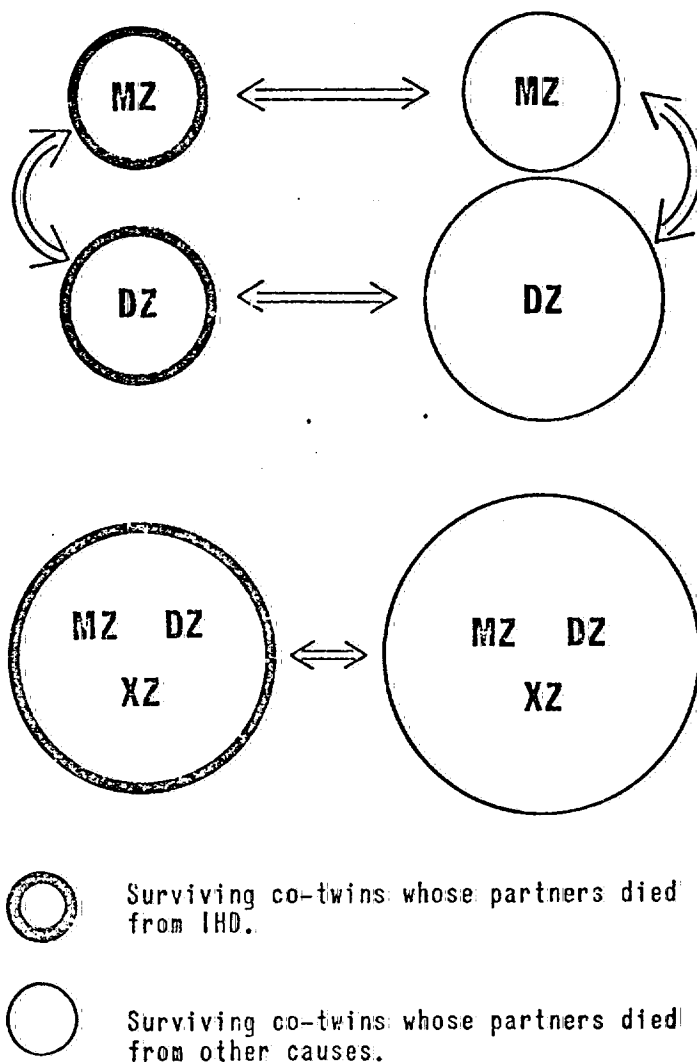


Fig. 6. Statistical comparisons between the various groups of surviving co-twins.

Conventional methods were used for the calculation of mean values (M) and standard error of the mean (SE). Significance of differences between mean values was tested by Student's t-test. Differences between proportions were tested in fourfold tables by Fisher's exact probability test. Differences between combinations of risk factors (Chapter III, section 4) were tested in two-by-k tables, using the chi-square test.

Intra-pair differences (the death discordant pairs) of qualitative variables such as smoking and registered abuse of alcohol (Chapter III, section 3) were examined by the use of tables of binomial probability distribution (McNemar, 1955). If the direction of the distribution could be expected, the one-tailed probability was calculated. Degrees of significance were tested at the levels of 5 % ( $p < 0.05$ ), 1 % ( $p < 0.01$ \*\*) and 0.1 % ( $p < 0.001$ \*\*\*).

1. I

This section  
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the survival

Material and

Questionnaire

The distribution  
according to the  
cardiac infarction

Table 8. Distribution of  
(absolute numbers)  
according to

Males	Angiogram
	performed
	Myocardial infarction
	Total number
Females	Angiogram
	performed
	Myocardial infarction
	Total number

### III RESULTS

#### 1. ISCHAEMIC HEART DISEASE AMONG THE SURVIVING CO-TWINS

This section deals with the prevalence of angina pectoris, myocardial infarction and electrocardiographic changes suggestive of IHD among the surviving co-twins.

Material and Methods: see Chapters I and II.

#### Questionnaire and case history findings

The distribution of angina pectoris as recorded by interview, according to the questionnaire proposed by Rose (1962), and that of myocardial infarction verified at hospital, are given in Table 8.

Table 8. Distribution of angina pectoris and myocardial infarction (absolute numbers and prevalence rates) among respondent co-twins according to cause of death of index-twin

		IHD				not IHD			
		MZ	DZ	XZ	Tot.	MZ	DZ	XZ	Tot.
		No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %
Males	Angina pectoris	1 10	2 8	- -	3 7	- -	1 2	- -	1 1
	Myocardial infarction	3 30	3 12	- -	6 15	1 4	1 2	- -	2 3
	Total number	10	25	5	40	25	42	1	68
Females	Angina pectoris	2 25	1 11	- -	3 18	- -	4 8	- -	4 5
	Myocardial infarction	- -	- -	- -	- -	- -	1 2	- -	1 1
	Total number	8	9	0	17	30	48	2	80

The prevalence of angina pectoris and myocardial infarction was higher among the male co-twins whose partners had died from IHD (7 % and 15 % respectively) than among those whose partners had some other cause of death (1 % and 3 % respectively); among the zygosity groups, the highest prevalence rates were found for the MZ co-twins whose partners had died from IHD (10 % and 30 % respectively). Among the female subjects, the prevalence of angina pectoris was likewise higher for the co-twins, whose partners had died from IHD (18 %), compared to those whose partner had died from other causes (5 %). None of these differences was statistically significant. Only one (1 %) of the females had had a myocardial infarction verified at hospital.

#### Comments

The diagnosis of angina pectoris established by interview according to the questionnaire by Rose (1962) has been found to have a high specificity and also a fairly good sensitivity when compared to clinical judgement (Rose, 1962; Heyden et al, 1971). However, some patients diagnosed as having angina pectoris show normal coronary arteriograms (Likoff et al, 1967; Kemp et al, 1967); this has been found especially among premenopausal women (Fowler, 1972). The reported prevalence of angina pectoris is about the same in men and women in several studies (Kannel et al, 1961; Kannel & Feinleib, 1972; Bengtsson, 1973) but the prognosis as to survival and progression to more serious coronary manifestations is particularly discouraging in men. The Framingham study showed that one in 4 men with angina pectoris can expect a coronary attack within 5 years compared to half the risk for women (Kannel & Feinleib, 1972). With regard to myocardial infarction, the prevalence is considerably higher among men (Dawber et al, 1957; Epstein et al, 1965; Hagerup & From Hansen, 1968).

In the present study, the prevalence of angina pectoris is higher among the women than the men, while the reverse is true of myocardial infarction. The surviving male co-twins whose partners died from IHD, display the highest prevalence of symptoms suggestive of manifest IHD and the rate is especially high among the MZ co-twins. This tendency is more marked for myocardial infarction verified at hospital. The same tendency applies to the women as regards angina pectoris. None of these tendencies, however, gave statistically significant differences. Owing to the relatively low prevalence of manifest IHD and the small number of MZ and DZ co-twins whose partners died from this cause, it is difficult to assess the significance of heredity in

manifest IHD represents hidden bene- diagnostic relatively of IHD and logical stu

#### ECG and X-ray

The distrib exercise ar according t et al, 1967 not coded i: ECG was rec- performed i: working cap: treated with lower on ave compared to the male MZ higher for male DZ co-t other causes cant. Part c differences volume among pleural char twins whose twins whose than their sity groups pooled fema ( $p < 0.01$ ). have signif MZ co-twins tendency am

manifest IHD. It has been said (Epstein, 1964) that manifest IHD represents only "the top of the iceberg" and that the additional cases hidden beneath the surface account for the relative insensitivity of diagnostic instruments. However, ECG during and after exercise is a relatively sensitive instrument for the detection of "silent" forms of IHD and is probably the best method in this respect for epidemiological studies (Blomqvist, 1971; Helfant et al, 1973; Åstrand, 1973).

#### ECG and X-ray findings

The distributions of certain ECG findings at rest and during or after exercise are shown in Tables 9 and 10. The findings have been tabulated according to the code numbers in the modified Minnesota code (Åstrand et al, 1967). ST depression, T wave negativity and ectopic beats were not coded in the 15 subjects who were on digitalis therapy. Resting ECG was recorded in all the co-twins but exercise tests could not be performed in 11 for various reasons (Table 11). The means for maximum working capacity ( $W_{max}$ ) and final heart rate in the co-twins not treated with digitalis are given in Table 12. Both parameters are lower on average for the co-twins whose partners had died from IHD compared to those whose partners had died from other causes. Among the male MZ co-twins, however, both  $W_{max}$  and final heart rate are higher for those with partners who died from IHD, while among the male DZ co-twins they are higher for those whose partners died from other causes than IHD. The differences were not statistically significant. Part of these intrazygosity differences is probably due to the differences in age. Table 13 shows the mean values for relative heart volume among the surviving co-twins. For technical reasons and/or pleural changes, no data are available for 3 female and 1 male DZ co-twins whose partners died from other causes than IHD. The male MZ co-twins whose partners died from IHD have larger relative heart volumes than their male DZ counterparts ( $p < 0.05$ ), but the pooled male zygosity groups (IHD vs not IHD) do not differ. On the other hand, the pooled female zygosity groups (IHD vs not IHD) differ significantly ( $p < 0.01$ ). The female MZ co-twins, with partners who died from IHD, have significantly ( $p < 0.05$ ) larger relative heart volumes than these MZ co-twins whose partners died from other causes. There is a similar tendency among the DZ females but the difference is not significant.

Table 9. Distribution of electrocardiographic changes at rest among respondent co-twins according to cause of death of index-twin.

	ECG code	Males								Females							
		MZ	IHD DZ	XZ	Tot.	MZ	not IHD DZ	XZ	Tot.	MZ	IHD DZ	XZ	Tot.	MZ	not IHD DZ	XZ	Tot.
Q-waves	1:1	1	2		3	1	1		2					1	1		2
	2	3	1		4					1			1	1		1	2
	3					2	4		6	2			2		3		3
Axis deviation left	2:1		4		4	2	2		4		1		1	1	4		5
High ampl. R-wave left type	3:1		2		2	1	2		3	1	1		2	2	2		4
	3	1	3	2	6		3		3	1			1	3	1		4
ST depression	4:1																
	2	1			1	3			3					2	2		4
	3	2	3	2	7	1	4		5	1	4		5	4	7	1	12
	4+5		7		7	3	4		7	4	1		5	5	10	1	16
	6+7		1		1	1			1								
T-wave																	
> -5 mm	5:1						1		1						1		1
-1 to -5 mm	2						1		3					1	3		4
Flat or diphasic	3	1			1	2	1		3								
Low amplitude	4	3	16	3	22	13	21		34	5	3		8	12	21	2	35
LBBB	7:1						1		1	1			1		1		1
Ectopic beats																	
ventric.	10:1-5	1		1	2	1	3		4		1		1	1	5	1	7
supraventric.	6-8			1	1										1	1	2
Digitalis therapy		2	2		4	3	2		5	2			2	3	1		4
Total examined		10	25	5	40	25	42	1	68	8	9		17	30	48	2	80

For Q-waves and ST depressions see appendix.

Table 10. Distribution of the most pronounced electrocardiographic changes during or after exercise among respondent co-twins according to cause of death of index-twin.

	ECG code	Males								Females							
		MZ	IHD DZ	XZ	Tot.	MZ	not IHD DZ	XZ	Tot.	MZ	IHD DZ	XZ	Tot.	MZ	not IHD DZ	XZ	Tot.
ST depression																	

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For Q-waves and ST depressions see appendix.

Table 10. Distribution of the most pronounced electrocardiographic changes during or after exercise among respondent co-twins according to cause of death of index-twin.

	ECG code	Males								Females							
		IHD				not IHD				IHD				not IHD			
		MZ	DZ	XZ	Tot.	MZ	DZ	XZ	Tot.	MZ	DZ	XZ	Tot.	MZ	DZ	XZ	Tot.
ST depression	4:1	2	4		6	3	1		4		2		2	2	2		4
	2	3	6	1	10	3	8		11	3	3		6	11	13	1	25
	3	2	4	2	8	3	10		13	3	3		6	7	16		23
	4+5		4		4	2	4	1	7		1		1	4	4		8
	6+7		2	1	3	3	6		9					3	3		6
T-wave																	
$\geq -5$ mm	5:1	1			1										1		1
-1 to -5 mm	2	1	1	1	3	1	1		2								
Flat or diphasic	3	1	2		3	1	1		2	2			2	5	4		9
Low amplitude	4	3	12	2	17	11	27	1	39	3	5		8	15	25		40
Ectopic beats																	
freq. ventric. 10:1-4				1	1		2		2	1			1	1	6	1	8
occasion. ventric. 5	4	4	1	9		4	5		9	1	3		4	3	9		12
supraventric. 6-8			2	2		1	3		4		2		2	2	5		7
Total number		8	23	4	35	19	39	1	59	6	9		15	27	45	1	73

For Q-waves and ST depressions see appendix.

Table 11. Distribution of respondent co-twins not performing the exercise test according to reason for non-performance.

	Males								Females							
	IHD				not IHD				IHD				not IHD			
	MX	DZ	XZ	Tot.	MZ	DZ	XZ	Tot.	MZ	DZ	XZ	Tot.	MZ	DZ	XZ	Tot.
Status post myocardial infarction	1			1									1			1
Cardiac insufficiency													1			1
Pacemaker			1	1												
Parkinsons' disease					1			1								
Status post poliomyelitis															1	1
Rectal cancer					1			1								
Orthopaedic reasons					1			1					2			2
Refusal							1	1								
Total number	1	1	2	4	3	1		4					1	3	1	5

Table 12. Distribution of means for  $W_{max}$  and final heart rate according to cause of death of index-twin (subjects on digitalis therapy omitted).

	Males								Females							
	IHD				not IHD				IHD				not IHD			
	MX	DZ	XZ	Tot.	MZ	DZ	XZ	Tot.	MZ	DZ	XZ	Tot.	MZ	DZ	XZ	Tot.

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Table 12. Distribution of means for Wmax and final heart rate according to cause of death of index-twin (subjects on digitalis therapy omitted).

	Males								Females							
	IHD				not IHD				IHD				not IHD			
	MZ	DZ	XZ	Tot.	MZ	DZ	XZ	Tot.	MZ	DZ	XZ	Tot.	MZ	DZ	XZ	Tot.
	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)
Wmax (kpm/min.)	647 (91)	621 (37)	675 (95)	633 (33)	636 (43)	692 (30)	150 (0)	664 (26)	404 (62)	428 (49)	-	418 (37)	432 (21)	427 (16)	400 (0)	428 (13)
Final heart rate (beats/min.)	158 (5.0)	148 (3.7)	158 (7.8)	152 (2.9)	150 (4.4)	157 (2.9)	146 (0.0)	155 (2.4)	149 (11.7)	153 (4.9)	-	152 (5.3)	158 (2.3)	153 (2.7)	118 (0.0)	155 (2.0)
Total number	8	23	4	35	19	39	1	59	6	9	-	15	27	45	1	73

Table 13. Distribution of means for heart volume among respondent co-twins according to cause of death of index-twin.

	Males								Females							
	IHD				not IHD				IHD				not IHD			
	MZ	DZ	XZ	Tot.	MZ	DZ	XZ	Tot.	MZ	DZ	XZ	Tot.	MZ	DZ	XZ	Tot.
	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)
Heart volume (cc/m <sup>2</sup> BSA)	449 (25)	384 (13)	462 (33)	410 (12)	413 (16)	407 (13)	520 (0)	411 (10)	430 (22)	397 (31)	-	412 (19)	368 (11)	353 (9)	400 (60)	360 (7)
Total number	10	25	5	40	25	41	1	67	8	9	-	17	30	45	2	77

BSA=Body surface area

ST-T changes have been omitted from the tables in the case of two anemic co-twins with a hemoglobin concentration below 10 g %. One of them, a female DZ co-twin, had been treated at hospital for hyperthyroidism and renal insufficiency and had a serum creatinine level of 3.6 mg %. Her partner had died from uraemia and the autopsy showed polycystic kidneys. The surviving co-twin has possibly also polycystic kidneys. The other, a male MZ co-twin whose brother had committed suicide, had signs of left ventricular hypertrophy with high amplitude R-wave (3:1) and ventricular activation time  $>0.05$  seconds. He also had an enlarged heart at X-ray, with a relative size of 600 ml per square metre body surface. He was diagnosed as having a suspect cardiomyopathy. These two subjects showed no clinical signs of IHD and their ST depressions (4:1-2) were not considered indicative of IHD.

Two of the co-twins displayed physical and phono-cardiographic signs of congenital heart disease and valvular heart disease respectively. One of them, a male MZ co-twin whose partner had died from asthma bronchiale, had dyspnoe on effort. He was treated with digitalis and the ECG showed intraventricular block. The probable diagnosis was atrial septal defect. The other co-twin, a female DZ whose partner had died from malignant tumor of the breast, revealed no symptoms of cardiac insufficiency. The ECG was normal. The probable diagnosis in this case was mitral insufficiency.

The cumulative distribution of different manifestations of IHD is given in Table 14. Myocardial infarction verified at hospital has been taken as the "hardest" criterion of IHD. Angina pectoris and various ECG criteria are then successively added to myocardial infarction. Figure 7 shows the prevalence of some of these combinations. The surviving co-twins whose partners died from IHD display a consistently higher prevalence of the various IHD manifestations than those whose partners died from other causes than IHD. This applies to both the male and the female groups but is somewhat more pronounced for the male, particularly when the assessment of IHD has been extended to include ST depressions. The difference between the male co-twins (MZ + DZ + XZ) whose partners did or did not die from IHD is statistically significant ( $p < 0.05$ ) not only when ST depressions  $\geq 1.0$  mm are included but also for ST depressions  $\geq 0.5$  mm. Comparing the prevalence of the various IHD manifestations within the zygosity groups, it is the MZ co-twins whose partners died from IHD, who are consistently the

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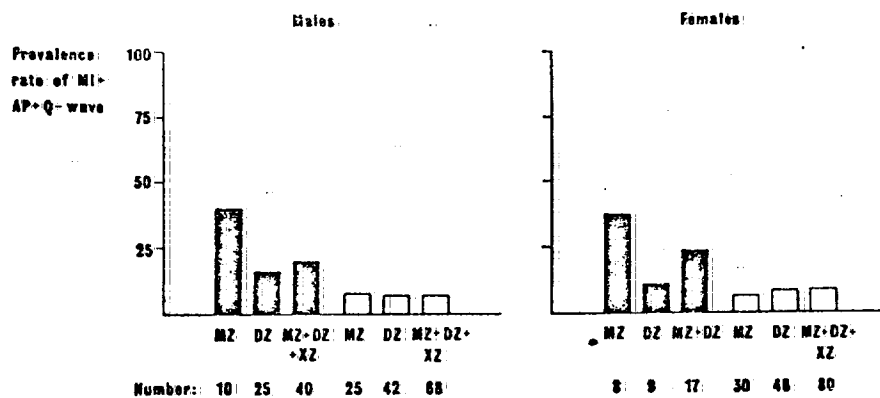
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Table 14. Cumulative distribution of different IHD manifestations among respondent co-twins according to cause of death of index-twin (code numbers within parentheses).

	Males								Females							
	IHD				not IHD				IHD				not IHD			
	MZ	DZ	XZ	Tot.	MZ	DZ	XZ	Tot.	MZ	DZ	XZ	Tot.	MZ	DZ	XZ	Tot.
Myocardial infarction	3	3		6	1	1		2							1	1
+ Angina pectoris	3	4		7	1	2		3	2	1		3			4	4
+ Q-wave (1:1-2)	4	4		8	2	3		5	3	1		4	2	4	1	7
+ ST depression (4:1-2) during/after exercise	7	13	1	21	6	12		18	5	5		10	15	16	2	33
+ T-wave (5:1-2) during/after exercise	7	13	1	21	6	12		18	5	5		10	15	16	2	33
+ Q-wave (1:3)	7	13	1	21	7	15		22	6	5		11	15	17	2	34
+ ST depression (4:3)	9	17	3	29	9	23		32	8	8		16	21	32	2	55
+ T-wave (5:3)	9	17	3	29	9	23		32	8	8		16	21	32	2	55
+ LBBB (7:1)	9	17	3	29	9	23		32	8	8		16	21	32	2	55
Total number	10	25	5	40	25	42	1	68	8	9		17	30	48	2	80

For Q-waves and ST depressions see appendix.

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most affected of IHD manifestations die from IHD. depressions >0.5 mm. Additionally more included, irregular difference be also significant

#### Comments

The clinical sudden death, epidemiologic, detect preclinical

Concerning tion. The spec by autopsy and co-twins with tion studies, Wilhelmsen, 19 Karvonen, 1973 of IHD. However seven countries power for future

ECG changes

considered to must be remembered IHD are others with angiography (response to ex IHD (Mattingly, Doyle & Kinch, directly dependent. A study by Dea step test, a m in detecting ST depression (Birnbeck, 1946; the frequency

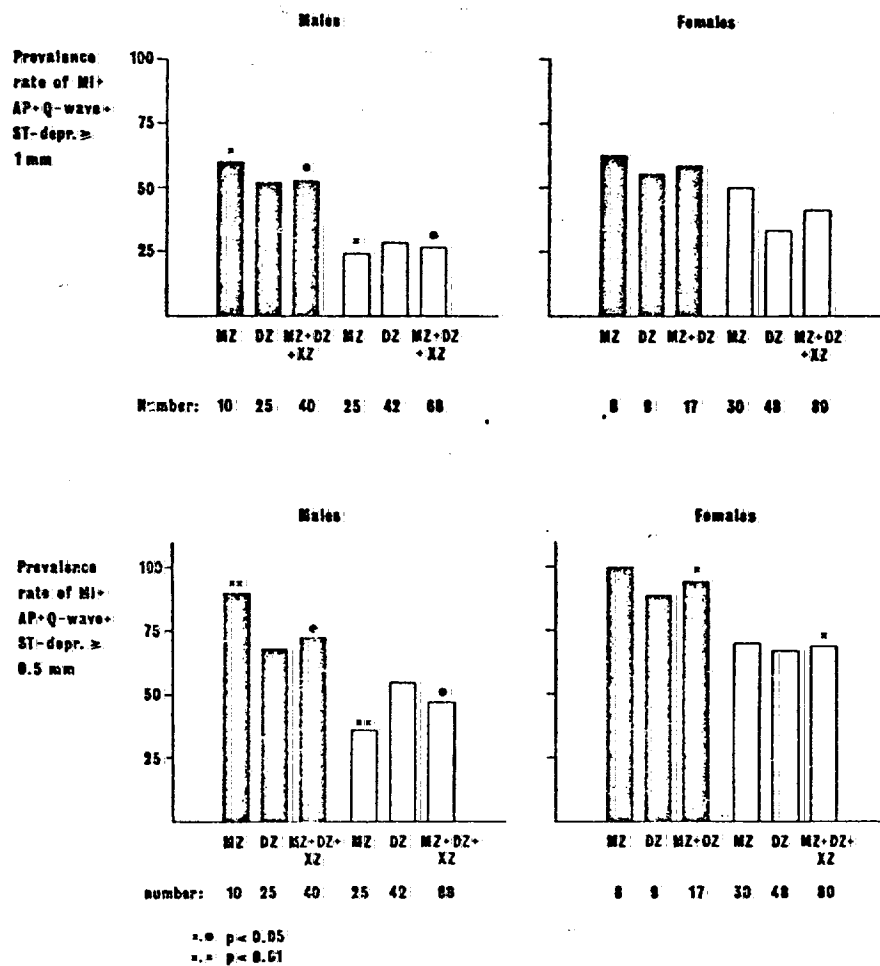


Fig. 7. Prevalence rate of some IHD manifestations among respondent co-twins. Dark columns indicate that the partner died from IHD and white columns that partner died from other causes.

most affected group. They have significantly higher prevalence rates of IHD manifestations than their counterparts whose partners did not die from IHD. The difference is significant at the 5 % level when ST depressions  $\geq 1.0$  mm are included and at the 1 % level when ST depressions  $\geq 0.5$  mm are included. The female co-twins seem to be proportionally more affected than the males when softer IHD criteria are included, irrespective of the cause of death (IHD/not IHD). The difference between the pooled female zygosity groups (IHD vs not IHD) is also significant ( $p < 0.05$ ) when ST depressions  $\geq 0.5$  mm are included.

#### Comments

The clinical entities myocardial infarction, angina pectoris and sudden death are usually included in the definition of IHD. Most epidemiological studies also include various ECG findings in order to detect preclinical cases of IHD.

Concerning Q-waves,  $Q_1$  is nearly always suggestive of old infarction. The specificity of  $Q_{1-2}$  as an indicator of IHD has been validated by autopsy and found to be high (Bjurulf et al, 1967). All the present co-twins with myocardial infarction had  $Q_1$  or  $Q_2$ . In several population studies,  $Q_{1-2}$  (Epstein et al, 1965; Rose, 1971; Tibblin & Wilhelmsen, 1971; Bengtsson, 1973) and sometimes  $Q_{1-3}$  (Punsar & Karvonen, 1973) have been taken as evidence of the probable presence of IHD. However, in a five year follow-up of nearly 13,000 men from seven countries, the presence of a  $Q_3$  had no significant prognostic power for future IHD (Blackburn et al, 1970).

ECG changes, mainly ST changes, in connection with exercise are considered to be useful for detecting preclinical forms of IHD. It must be remembered, however, that some subjects with clinically documented IHD display no ECG abnormality at exercise, just as there are others with abnormal ECG response at exercise and normal coronary angiography (Redwood & Epstein, 1972). ST segmental depressions in response to exercise has been shown to be a good predictor of overt IHD (Mattingly, 1962; Åstrand & Lundman, 1968; Blackburn et al, 1970; Doyle & Kinch, 1970). The order of ST segmental depressions is also directly dependent on the relative load at exercise (Blomquist, 1965). A study by Doan et al (1965) showed that, compared to Master's two-step test, a near-maximal test increased the sensitivity nine times in detecting ischaemic ST depressions.

ST depressions seem to be a less specific sign of IHD in women (Börck, 1946; Lepeschkin, 1958; Åstrand, 1965). Åstrand noted that the frequency of ST depressions  $\geq 0.5$  mm among men should be about

20 % at 55 years of age and about 35 % at 60. For females, the expected frequency should be about 50 % at 55 years and over. These figures are based upon submaximal work load with fixed target pulse for different age-groups (Åstrand et al, 1967). In the present study too, ST depressions were more common among the women.

When ST depressions were included in the criteria suggesting IHD, the surviving male co-twins with partners who died from IHD displayed these signs of IHD significantly more often than those whose partners died from other causes. These findings go in the same direction as those of Liljefors (1970) for 91 male twin pairs. An extension of the ECG criteria of IHD to ST depressions  $\geq 0.5$  mm among females also significantly ( $p < 0.05$ ) discriminates co-twins whose partners died from IHD from those whose partners died from other causes. In some studies (Epstein et al, 1965; Bengtsson, 1973) ST depressions have not been coded in the presence of high amplitude R-waves (3:1) because in such cases ST depressions were considered to reflect a hypertensive disease. If this procedure had been adopted in this study, the significant differences ( $p < 0.05$ ) in IHD manifestations between the surviving female co-twins would have been non-significant but the significances recorded between the male co-twins would have been unchanged. However, experience from the Framingham study has shown that left ventricular hypertrophy (including ST depression and T-wave inversion) predicts the IHD incidence over and above what could be accounted for by the concurrent hypertension (Kannel et al, 1970; Dawber & Kannel, 1972). They considered these abnormalities to reflect not only a hypertensive hypertrophy but also IHD.

The differences recorded in IHD manifestations certainly reflect a genetic influence, which is furthermore underlined by the striking differences in IHD manifestations in spite of a reversed age factor between the male MZ co-twins whose partners did or did not die from IHD. The possible role of environmental factors is discussed in some of the subsequent chapters.

## 2. BIONOMETRIC THE SURVIVIN

### ANTHROPOMETR

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## 2. BIOMETRIC FACTORS ASSOCIATED WITH ISCHAEMIC HEART DISEASE AMONG THE SURVIVING CO-TWINS

### ANTHROPOMETRIC VARIABLES

Obesity is usually defined in terms of weight and then compared to standards or norms for the entire population or expressed as relative weight. Another measure of obesity is skin-fold thickness.

Obesity is generally considered to involve a substantial risk of IHD, though the relationship is somewhat unclear. In the Tecumseh study, the prevalence of IHD was independently correlated with overweight among men, but not among women (Epstein et al, 1965). The Framingham study has shown an association between overweight and an increased incidence of angina pectoris and sudden death but not myocardial infarction (Kannel et al, 1967). Multivariate analysis of the data from the seven country study (Keys et al, 1972) showed that no measure of relative weight or obesity made a significant contribution to future IHD, when the factors of age, blood pressure, serum cholesterol, and smoking were comparable.

Gertler & White (1954) found no differences in weight between controls and men under 40 with previous myocardial infarction. The mesomorphic body build was, however, more common among the infarction group than among the controls. Forssman & Lindegård (1958) studied a similar material of post-infarction men under 56. They distinguished between two sub-groups in the material, one with above average length, weight and sturdiness factors, and the other with small such factors. In an autopsy study by Bjurulf (1959) on 110 patients, aged 25-88, 19 of whom had myocardial infarction, the severity of coronary atherosclerosis was correlated to the size of the subcutaneous fat cells, but not to their number, and also to the muscle mass. It was concluded that the grade of coronary atherosclerosis was more dependent on environmental influence than on genetic disposition. The results from a study by Björntorp & Sjöström (1971) also suggest two forms of obesity. One is characterized by a hypertrophy of fat cells and is of a moderate degree. This type of obesity has been shown to be associated with metabolic disturbances. The other form has an increased number of fat cells and is associated with much more severe obesity. In a comparison between post-infarction males and controls, Berchtold et al (1972) found no difference with regard to body fat and fat cell size. In a study on women, Bengtsson (1973) reported no significant

difference with regard to overweight between control groups and women with myocardial infarction, angina pectoris and ECG signs suggestive of IHD respectively. In another study (Cramér et al, 1966) on 173 males and 51 females, no correlation was found between coronary angiographic findings and relative weight.

It must be born in mind, however, that obese persons are more likely to be hypertensive and hyperlipidaemic, hyperglycaemic and hyperuricaemic and that this probably reflects chronic caloric imbalance in susceptible people (Stamler, 1973).

Material and Methods: see Chapters I and II.

### Results

The distribution of the means of some of the anthropometric parameters is shown in Table 15. There are no substantial differences among the males. The MZ co-twins whose partners died from IHD are somewhat heavier and have a bigger arm circumference as well as more skinfold fat in the triceps area than either the DZ co-twins with IHD partners or the MZ co-twins whose partners died of other causes than IHD. These differences are not statistically significant. The female co-twins, especially the MZ group, whose partners died from IHD are heavier and have somewhat more skinfold fat than the co-twins whose partners died from other causes than IHD, but these differences are not statistically significant. The distribution of "overweight" co-twins, defined as a relative weight  $\geq 110$  according to the earlier described weight/height index, is shown in Table 16. Of the male co-twins whose partners died from IHD, 18 % are "overweight" compared to 24 % of those whose partners died from other causes. The corresponding figures among the females are 53 % and 46 %. None of the differences with regard to the occurrence of "overweight" is statistically significant.

### Comments

Height and skeletal measurements were found to be chiefly dependent on genetic factors in twin studies by Osborne & de George (1959) and Takkunen (1964). On the other hand Lundman (1966) and Liljefors (1970) in their twin studies found weight and skinfold thickness to be dependent on both genetic and environmental factors. The co-twins whose partners died from IHD displayed a tendency to greater relative weight and skinfold fat compared to those whose partners died from other causes. This was more marked among the females, especially the MZ co-twins. The finding could indicate that these parameters in some measure are linked to the development of IHD in females.

Table 15. Distribution of means for some anthropometric parameters of respondent co-twins according to cause of death of index-twin.

	Males		Females	
	IHD	not IHD	IHD	not IHD

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Table 15. Distribution of means for some anthropometric parameters of respondent co-twins according to cause of death of index-twin.

	Males								Females							
	IHD				not IHD				IHD				not IHD			
	MZ	DZ	XZ	Tot.	MZ	DZ	XZ	Tot.	MZ	DZ	XZ	Tot.	MZ	DZ	XZ	Tot.
	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)
A.	173.7 (1.4)	173.1 (0.9)	172.8 (1.8)	173.2 (0.7)	173.2 (1.1)	171.0 (1.1)	170.0 0	171.8 (0.8)	156.9 (2.2)	163.8 (1.5)	-	160.5 (1.5)	158.7 (1.1)	159.5 (0.9)	155.0 (2.0)	159.1 (0.7)
B.	75.6 (3.1)	72.2 (1.8)	72.4 (2.0)	73.1 (1.4)	71.9 (2.4)	72.1 (1.5)	64.0 0	71.9 (1.3)	70.1 (7.2)	71.3 (4.6)	-	70.8 (4.0)	62.0 (1.5)	66.1 (1.9)	76.0 (6.0)	64.8 (1.3)
C.	11.4 (1.8)	9.6 (0.6)	9.0 (1.4)	10.0 (0.6)	9.0 (0.7)	9.8 (0.4)	10.0 0	9.5 (0.4)	23.1 (1.9)	20.0 (2.0)	-	21.4 (1.4)	19.4 (1.0)	19.3 (0.7)	20.3 (3.3)	19.3 (0.5)
D.	15.9 (1.6)	15.6 (1.1)	15.8 (1.1)	15.7 (0.8)	15.9 (1.3)	16.3 (1.0)	13.2 0	16.1 (0.7)	24.0 (3.4)	21.4 (2.8)	-	22.6 (2.1)	18.4 (1.3)	20.8 (1.2)	31.6 (2.6)	20.2 (0.9)
E.	31.4 (1.0)	30.0 (0.5)	30.1 (0.3)	30.4 (0.4)	30.0 (0.7)	30.4 (0.4)	28.0 0	30.2 (0.3)	32.0 (1.9)	31.7 (1.3)	-	31.8 (1.1)	29.8 (0.6)	30.3 (0.8)	33.3 (0.3)	30.2 (0.5)
F.	103 (4.3)	99 (2.4)	100 (2.5)	100 (1.9)	98 (3.2)	101 (1.7)	91 0	100 (1.6)	122 (8.3)	112 (7.3)	-	117 (5.4)	107 (3.3)	111 (2.8)	139 (16.0)	110 (2.2)
Tot.	10	25	5	40	25	42	1	68	8	9	-	17	30	48	2	80

A=Height, cm; B=Weight, kg; C=Skinfold, triceps area mm; D=Skinfold, subscapular area mm; E=Arm circumference, cm; F=Relative weight.

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Table 16. Distribution of respondent co-twins with "overweight" (relative weight  $\geq 110$ ) according to cause of death of index-twin.

	IHD				not IHD			
	MZ No. %	DZ No. %	XZ No. %	Tot. No. %	MZ No. %	DZ No. %	XZ No. %	Tot. No. %
"Overweight" males (relative weight $\geq 110$ )	3(30)	4(16)	0	7(18)	7(28)	9(21)	0	16(24)
Total number	10	25	5	40	25	42	1	68
"Overweight" females (relative weight $\geq 110$ )	4(50)	5(56)	-	9(53)	11(37)	24(50)	2(100)	37(46)
Total number	8	9	-	17	30	48	2	80

#### BLOOD PRESSURE

Elevated blood pressure has been designated one of the major risk factors for premature IHD (Atherosclerosis Study Group, 1970; Simborg, 1970; Stamler & Epstein, 1972; Stamler, 1973). Data from 14 years follow-up of 5,127 men and women in the Framingham study (Kannel et al, 1971) have shown that the risk of developing IHD is simply proportional to blood pressure from the lowest to the highest level for both men and women. Furthermore, similar gradients of risk were observed whether persons were classified by their systolic or diastolic pressure although the systolic pressure displayed a stronger association with the risk of developing IHD.

According to Epstein (1964), familial aggregations of IHD seem to be conditioned to some extent by hypertension, which could thus be one of the mechanisms of genetic transmission. A genetic influence has been demonstrated for essential hypertension in family studies and studies on twins, extensively reviewed by Miall (1971), who supports the hypothesis that arterial pressures are determined polygenically. He also notes that familial factors account for only one third of the variance of systolic pressure and one fifth of that of diastolic and that non-familial environmental factors presumably account for the remainder.

Some of the twin studies by Osborne et al (1963), Downie et al (1969), and Liljefors (1970) have shown blood pressure to be pre-

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dominantly under environmental influence, as elucidated from comparisons between MZ and DZ intra-pair variances, whereas studies by Takkenen (1964) and Lundman (1966) have pointed to a stronger genetic influence. Genetic factors also seem to play a more important role in females, to judge from the studies by Lundman and Osborne et al.

Material and Methods: see Chapters I and II.

### Results

The distribution of means for casual and basal blood pressure and pulse rates is shown in Tables 17 and 18. Casual and basal systolic pressures as well as diastolic phase 4 and 5 pressures are on average higher for the co-twins with partners who died from IHD than for those whose partners died from other causes. The differences are relatively marked among the females, especially for casual systolic pressure, where the difference is significant ( $p < 0.05$ ). Comparisons by zygosity show that the male MZ co-twins whose partners died from IHD display a slight tendency to have higher measured pressures than the DZ co-twins in this IHD group. For the females there is the reverse tendency for casual pressures, the DZ co-twins having the highest values. The casual systolic pressures are also significantly ( $p < 0.05$ ) higher for the female DZ co-twins whose partners died from IHD than the female DZ co-twins whose partners died from other causes than IHD. The distribution of co-twins with elevated blood pressure, defined here as basal systolic  $\geq 160$  mm Hg and/or  $\geq 95$  mm Hg diastolic phase 4, is presented in Table 19. The occurrence of "hypertension" according to this definition is 48 % among the male co-twins with partners who died from IHD and 41 % among those whose partners died from other causes, the corresponding figures for the females being 59 % and 41 %. None of the differences is statistically significant.

### Comments

Population studies concerning blood pressure, extensively reviewed by Tibblin (1967), show that blood pressure rises with age, that the systolic pressure increases more than the diastolic after 50 and that blood pressure in old women is higher than in old men. In the present investigation the blood pressures, especially the casual systolic, are surprisingly high in the females whose partners had died from IHD. To some extent this could possibly be explained by the fact that they were on average 4 years older as well as heavier than the female co-twins whose partners had died from other causes than IHD. It has been found

Table 17. Distribution of means for casual blood pressure (B.p.) and pulse rate in respondent co-twins according to cause of death of index-twin.

Males								Females							
IHD				not IHD				IHD				not IHD			
MZ	DZ	XZ	Tot.	MZ	DZ	XZ	Tot.	MZ	DZ	XZ	Tot.	MZ	DZ	XZ	Tot.
M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)
A. 167.5	166.0	147.0	164.0	163.0	157.6	170.0	159.8	191.3	199.4	-	195.6	175.7	172.1	192.5	174.0
(10.9)	(5.9)	(6.8)	(4.7)	(5.5)	(3.4)	0	(2.9)	(12.5)	(7.2)	-	(6.8)	(7.1)	(4.9)	(2.5)	(4.0)
B. 99.5	96.0	88.0	95.9	93.0	93.0	95.0	93.0	98.1	100.0	-	99.1	94.0	93.5	112.5	94.2
(4.4)	(2.2)	(4.6)	(1.9)	(2.3)	(1.5)	0	(1.2)	(4.6)	(3.8)	-	(2.9)	(2.8)	(2.3)	(12.5)	(1.8)
C. 98.0	95.4	88.0	95.1	91.6	92.1	95.0	92.0	97.5	100.0	-	98.8	92.0	91.7	112.5	92.3
(4.2)	(2.3)	(4.6)	(1.9)	(2.4)	(1.5)	0	(1.3)	(4.4)	(3.8)	-	(2.8)	(2.8)	(2.4)	(12.5)	(1.8)
D. 81.4	76.5	66.0	76.4	75.6	77.8	68.0	76.9	78.3	78.0	-	78.1	83.9	83.4	79.0	83.5
(4.5)	(2.9)	(3.8)	(2.3)	(2.9)	(2.3)	0	(1.8)	(5.3)	(4.8)	-	(3.4)	(3.3)	(2.4)	(19.0)	(1.9)
Tot. 10	25	5	40	25	42	1	68	8	9	-	17	30	48	2	80

A=Systemic B.p.; B=Diastolic B.p., phase 4; C=Diastolic B.p., phase 5; D=Pulse rate, beats/min.

Table 18. Distribution of means for basal blood pressure (B.p.) and pulse rate in respondent co-twins according to cause of death of index-twin.

Males								Females							
IHD				not IHD				IHD				not IHD			
MZ	DZ	XZ	Tot.	MZ	DZ	XZ	Tot.	MZ	DZ	XZ	Tot.	MZ	DZ	XZ	Tot.
M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M

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Table 18. Distribution of means for basal blood pressure (B.p.) and pulse rate in respondent co-twins according to cause of death of index-twin.

	Males								Females							
	IHD				not IHD				IHD				not IHD			
	MZ M (SE)	DZ M (SE)	XZ M (SE)	Tot. M (SE)	MZ M (SE)	DZ M (SE)	XZ M (SE)	Tot. M (SE)	MZ M (SE)	DZ M (SE)	XZ M (SE)	Tot. M (SE)	MZ M (SE)	DZ M (SE)	XZ M (SE)	Tot. M (SE)
A.	154.5 (11.6)	147.2 (5.0)	137.0 (7.5)	147.8 (4.3)	147.0 (4.7)	140.5 (2.6)	150.0 0	143.0 (2.4)	172.5 (13.2)	166.1 (7.3)	-	169.1 (7.1)	152.3 (5.7)	154.4 (4.7)	175.0 (10.0)	154.1 (3.5)
B.	97.0 (5.2)	91.4 (1.6)	85.0 (5.7)	92.0 (1.8)	90.2 (2.6)	88.8 (1.3)	95.0 0	89.4 (1.2)	94.4 (4.2)	89.4 (3.7)	-	91.8 (2.7)	86.8 (2.5)	88.1 (2.1)	112.5 (12.5)	88.3 (1.6)
C.	95.0 (4.6)	90.8 (1.7)	85.0 (5.7)	91.1 (1.7)	89.6 (2.6)	87.5 (1.5)	95.0 0	88.4 (1.3)	93.8 (4.2)	88.9 (3.8)	-	91.2 (2.8)	85.7 (2.6)	87.0 (2.1)	110.0 (10.0)	87.1 (1.6)
D.	75.0 (3.5)	71.8 (2.3)	62.8 (4.2)	71.5 (1.8)	71.8 (2.5)	74.2 (2.3)	68.0 0	73.2 (1.7)	70.8 (4.1)	68.2 (3.6)	-	69.4 (2.6)	77.4 (2.9)	76.5 (1.9)	72.0 (8.0)	76.7 (1.6)
Tot.	10	25	5	40	25	42	1	68	8	9	-	17	30	48	2	80

A=Systolic B.p.; B=Diastolic B.p, phase 4; C=Diastolic B.p., phase 5; D=Pulse rate, beats/min.

Table 19. Distribution of respondent co-twins with elevated basal blood pressure ( $\geq 160$  mm Hg systolic and/or  $\geq 95$  mm Hg diastolic, phase 4).

Elevated blood pressure	IHD				not IHD			
	MZ No. %	DZ No. %	XZ No. %	Tot. No. %	MZ No. %	DZ No. %	XZ No. %	Tot. No. %
Males	6(60)	12(48)	1(20)	19(48)	12(48)	15(57)	1(100)	28(41)
Tot.	10	25	5	40	25	42	1	68
Females	5(63)	5(56)	-	10(59)	16(53)	15(31)	2(100)	33(41)
Tot.	8	9	-	17	30	48	2	80

(Humerfeldt, 1963) that when age is held constant, systolic blood pressure increases only about 3 mm Hg for each 10 kg increase in weight and diastolic blood pressure only 2 mm Hg. The twin studies mentioned earlier suggest that the genetic influence on blood pressure may increase with age and may be greater in women. The present co-twins whose partners died from IHD display a slight tendency to higher blood pressure and the highest values occur in the MZ co-twins except in the case of casual systolic and diastolic pressures in the females, where the highest values come from the DZ co-twins. ECG signs indicative of IHD were found by Bengtsson (1973) to be fairly unreliable in this respect and it was considered that in women they could probably be caused by hypertension. It is thus conceivable that the relatively high blood pressures recorded in the female co-twins whose partners died from IHD are partly responsible for the high prevalence of ECG signs suggestive of IHD.

#### LIPIDS

Cholesterol, like hypertension, has been designated one of the major risk factors for premature IHD (Atherosclerosis Study Group, 1970; Simborg, 1970; Stamler & Epstein, 1972; Stamler, 1973). The average serum cholesterol level of persons with myocardial infarction is higher than in the normal population (Björck et al, 1957; Carlson, 1960; Gustafsson et al, 1972) and several prospective studies have demonstrated strong statistical associations between elevated serum cholesterol and IHD in men (Keys et al, 1970; Rosenman et al, 1970; Kannel et al, 1971; Westlund & Nicolaysen, 1972). The Framingham study has shown that elevated serum cholesterol in women under 50 is associated

with an increased cholesterol level (Carlson et al, 1967).

Fewer Prospective studies (Carlson et al, 1967) have shown triglyceride levels as compared to represent angina pectoris.

Lipoprotein ultracentrifugation & Lees, 1967) number of and co-workers have shown that the risk of IHD is increased by an autosomal recessive homozygous state. The primary defect is only the general population (101 young men, 1973), there were signs in the infarcted times, hyperlipidaemia controls, premature not be as environmental. Some of serum cholesterol (Osborne et al, 1965; Kannel et al, 1971) indicating

with an increased risk of developing IHD (Kannel et al, 1971). Elevated cholesterol has also been found in women with manifest IHD (Mulcahy et al, 1967).

Fewer reports have been published on serum triglycerides and IHD. Prospective studies have shown that elevated triglycerides are likewise associated with an increased risk of myocardial infarction (Carlson & Böttiger, 1972; Tibblin, 1972). Significantly higher serum triglycerides were found by Bengtsson (1973) in women who had had myocardial infarction and in women with ECG changes suggestive of IHD as compared to the general female population. No significant overrepresentation of high serum triglycerides was found in women with angina pectoris.

Lipoproteins can be classified (Beaumont et al, 1970) by means of ultracentrifugation (Gofman et al, 1954) or electrophoresis (Fredrickson & Lees, 1965). Applying their lipoprotein phenotyping system to a large number of persons with a primary increase in plasma lipids, Fredrickson and co-workers managed to distinguish between five primary hyperlipoproteinaemias. Three of them (II-IV) are associated with an increased risk of IHD. Of the established hyperlipoproteinaemias, the classical familial hypercholesterolaemia (type II a) is thought to be inherited by an autosomal dominant gene with a high penetrance; it can occur in a homozygotic form (Fredrickson, 1971; Leading article, Lancet, 1971). The primary familial hyperlipoproteinaemias, however, usually include only the gross hyperlipidaemic cases, which are fairly uncommon in the general population. In a recent study on 412 first-degree relatives of 101 young survivors of myocardial infarction (Nikkilä & Aro, 1973; Aro, 1973), the mean levels of serum cholesterol and serum triglycerides were significantly higher than in a control population but lower than in the index patients. Hypercholesterolaemia (type II a) occurred 1.8 times, hypertriglyceridaemia (type IV) 1.3 times, and combined hyperlipidaemia (type II b) 2.5 times more frequently in relatives than in controls. It was furthermore concluded that one-third of patients with premature IHD have a familial trait of hyperlipidaemia, but it could not be established whether this trait is inherited or produced by environmental factors.

Some of the earlier twin studies have shown that the variability of serum cholesterol is due to both environmental and genetic factors (Osborne et al, 1959; Mc. Donough et al, 1962; Meyer, 1962; Jensen et al, 1965; Rifkind et al, 1968). Comparisons between twins living together and apart showed a smaller intra-pair variance among the former, indicating an influence from the environment. But as the intra-pair

difference was significantly greater for the DZ than the MZ pairs, there seems to be a genetic influence, too.

However, the study by Gedda & Poggi (1960) on twin pairs below the age of 20 showed that genetic factors strongly influenced the variability of cholesterol. In his study on 196 smoking discordant male and female twin pairs, using the Swedish Twin Registry, Lundman (1966) found cholesterol to be under both environmental and genetic influence, while for triglycerides and phospholipids the genetic component was more obvious in the female pairs. Studying 91 male twin pairs, Liljefors (1970) found evidence of a genetic influence on the cholesterol level from the significantly smaller variance in the MZ than the DZ twins. There was no such evidence of heredity in respect of triglycerides.

Material and Methods: see Chapters I and II.

### Results

The means for cholesterol and triglycerides are given in Table 20. Because the triglyceride values showed a skewed distribution they were transformed to their logarithms before making statistical comparisons. Both the cholesterol and the triglyceride values are higher on average for the male co-twins whose partners died from IHD than for those, whose partners died from other causes. The difference is not statistically significant. The highest lipid values among the male co-twins are those of the DZ co-twins whose partners died from IHD. Among the female co-twins there is a similar trend for cholesterol, with higher means for the co-twins, with partners who died from IHD. The trend for triglycerides is the reverse of this, mainly due to comparatively low values among the DZ co-twins whose partners died from IHD. None of the differences within the various male and female groups is statistically significant.

The distribution of co-twins with elevated cholesterol ( $\geq 250$  mg/100 ml) and/or elevated triglycerides ( $\geq 150$  mg/100 ml) is given in Table 21. Of the male co-twins whose partners died from IHD, 60 % had elevated cholesterol and/or triglyceride values compared to 50 % of those whose partners died from other causes. Among the female co-twins the corresponding figures were 76 % vs 68 %. None of the differences is statistically significant.

### Comments

Men and women often have much the same cholesterol levels from 20-50

Table 20. Distribution of means for cholesterol and triglycerides in respondent co-twins according to cause of death of index-twin.

Males						Females					
MZ	DZ	XZ	Tot.	M	N	MZ	DZ	XZ	Tot.	M	N
IHD						IHD					
				(SE)						(SE)	
not IHD						not IHD					
				(SE)						(SE)	
Tot.						Tot.					
				(SE)						(SE)	

Table 20. Distribution of means for cholesterol and triglycerides in respondent co-twins according to cause of death of index-twin.

Males								Females							
IHD				not IHD				IHD				not IHD			
MZ	DZ	XZ	Tot.	MZ	DZ	XZ	Tot.	MZ	DZ	XZ	Tot.	MZ	DZ	XZ	Tot.
M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)
A. 221.0	239.6	214.0	231.8	210.6	226.5	280.0	221.5	280.9	272.2	-	276.3	269.0	243.5	307.5	254.7
(8.4)	(11.8)	(20.0)	(8.1)	(9.2)	(8.0)	0	(6.1)	(35.2)	(21.8)	-	(19.5)	(9.6)	(8.7)	(17.5)	(6.5)
B. 127.5	167.8	151.0	155.6	144.8	137.4	110.0	139.7	168.1	117.8	-	141.5	150.5	157.7	175.0	155.4
(17.8)	(18.9)	(27.4)	(13.2)	(14.1)	(11.1)	0	(8.5)	(28.2)	(9.9)	-	(15.1)	(15.0)	(17.8)	(30.0)	(12.0)
C. 2.06	2.17	2.14	2.14	2.12	2.09	2.04	2.10	2.19	2.06	-	2.12	2.13	2.14	2.24	2.14
(0.07)	(0.04)	(0.10)	(0.04)	(0.04)	(0.03)	0	(0.02)	(0.07)	(0.05)	-	(0.04)	(0.04)	(0.03)	(0.08)	(0.02)
Tot. 10	25	5	40	25	42	1	68	8	9	-	17	30	48	2	80

A=Cholesterol (mg/100 ml); B=Triglycerides (mg/100 ml); C=Log triglycerides (mg/100 ml).

Table 21. Distribution of respondent co-twins with elevated cholesterol ( $\geq 250$  mg/100 ml) and/or elevated triglycerides ( $\geq 150$  mg/100 ml).

	Males								Females							
	IHD				not IHD				IHD				not IHD			
	MZ No. (%)	DZ No. (%)	XZ No. (%)	Tot. No. (%)	MZ No. (%)	DZ No. (%)	XZ No. (%)	Tot. No. (%)	MZ No. (%)	DZ No. (%)	XZ No. (%)	Tot. No. (%)	MZ No. (%)	DZ No. (%)	XZ No. (%)	Tot. No. (%)
Cholesterol $\geq 250$ mg/100 ml	0	6	1	7	2	9	1	12	3	5	-	8	11	10	1	22
Triglycerides $< 150$ mg/100 ml		(24)	(20)	(18)	(8)	(21)	(100)	(18)	(38)	(56)		(47)	(37)	(21)	(50)	(28)
Cholesterol $< 250$ mg/100 ml	4	2	2	8	6	10	0	16	1	0	-	1	2	9	0	11
Triglycerides $\geq 150$ mg/100 ml	(40)	(8)	(40)	(20)	(24)	(24)		(24)	(13)			(6)	(7)	(19)		(14)
Cholesterol $\geq 250$ mg/100 ml	2	7	0	9	4	2	0	6	3	1	-	4	9	11	1	21
Triglycerides $\geq 150$ mg/100 ml	(20)	(28)		(23)	(16)	(5)		(9)	(38)	(11)		(24)	(30)	(23)	(50)	(26)
Cholesterol $\geq 250$ mg/100 ml and/or triglycerides $\geq 150$ mg/ 100 ml	6	15	3	24	12	21	1	34	7	6	-	13	22	30	2	54
	(60)	(60)	(60)	(60)	(48)	(50)	(100)	(50)	(88)	(67)		(76)	(73)	(63)	(100)	(68)
Tot.	10	25	5	40	25	42	1	68	8	9	-	17	30	48	2	80

years of age. The triglyceride also well known (1970). In the with age in boys off in men but (Sjoberg, 1977 difference in partners died of the age difference in showed only a males but high the MZ twins; younger than showed the same reverse trend some of the di groups were r. The cut-off and/or triglyceride well known the factors. In the value over 250 high as the re Stockholm Pros linear relative cholesterol co

#### DIABETES, NUTRITION

The association between overt diabetes and higher insulin (Kannel et al, 1963; Kahnberg et al had abnormal (Kahnberg, 1963

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years of age but after that the values tend to be higher in females. The triglyceride level is usually lower in females than males. It is also well known that lipid levels increase with age (Beaumont et al, 1970). In the U.S.A., the average serum cholesterol level increases with age in both men and women until about 40 years, when it levels off in men but continues to rise in women until about 60 years of age (Simborg, 1970). In view of these findings, it is possible that the difference in cholesterol values between the female co-twins whose partners died or did not die from IHD is to some extent a reflection of the age difference (4 years). The twin study by Lundman (1966) showed only a weak association between age and serum lipid levels in males but highly significant correlations in females, especially among the MZ twins; the subjects, however, were on average about 10 years younger than the twins in the present investigation. Triglycerides showed the same trends as cholesterol among the male co-twins but the reverse trend among the females. However, it must be born in mind that some of the differences could be due to random variation because the groups were relatively small, especially the female "IHD groups".

The cut-off points used here to denote elevation of cholesterol and/or triglycerides have been chosen fairly liberally. It is, however, well known that there is no evidence of a critical level for these factors. In the Pooling Project in the U.S.A., men with a cholesterol value over 250 mg/100 ml carried a 10-year IHD risk about twice as high as the remainder of the population (Stamler & Epstein, 1972). The Stockholm Prospective Study (Carlson & Böttiger, 1972) also shows a linear relation to risk over the entire range of triglyceride and cholesterol concentrations.

#### DIABETES MELLITUS

The association between diabetes mellitus and IHD has long been recognized. An increased incidence of IHD is found not only in persons with overt diabetes mellitus but also in those with impaired glucose tolerance (Ostrander et al, 1965; Epstein, 1967). The Framingham data show a higher incidence of IHD in diabetic women than in diabetic men (Kannel et al, 1967). Conversely, a high proportion of subjects with IHD were found to have diabetes mellitus (Sievers et al, 1961, Sievers, 1963; Wahlberg, 1966; Simborg, 1970). Survivors of myocardial infarction had abnormal intravenous glucose tolerance more often than controls (Wahlberg, 1966). There seems to be general agreement on the hereditary

character of diabetes mellitus (Gedda & Brenchi, 1970), although this has been difficult to assess in population studies (Epstein, 1964). However, twin studies have shown considerably higher concordance regarding diabetes mellitus in MZ pairs compared to DZ pairs (Then Berg, 1938; von Verschuer, 1958; Joslin et al, 1959; Harvald & Hauge, 1965). In a study on MZ twins discordant with respect to overt diabetes mellitus Cerasi & Luft (1967) found a closely similar insulin response after glucose infusion, indicating a genetic influence.

Material and Methods: see Chapters I and II.

### Results

The prevalence rates for diabetes mellitus diagnosed earlier and the combination of this and fasting blood sugar  $>100$  mg/100 ml are about the same for the male co-twins irrespective of the cause of death of the partner (IHD/not IHD) (Table 22). The prevalence of overt diabetes mellitus is especially high among the MZ co-twins whose partners had not died from IHD (20 %) and it differs significantly ( $p < 0.05$ ) from the prevalence (0 %) among the DZ co-twins in the same group. However, it is worth noting that the 5 MZ co-twins whose partners died from other causes than IHD, who had diabetes mellitus, were all concordant in this respect, i.e. their deceased partners had also had overt diabetes mellitus, but this was not the cause of death in any of these

Table 22. Prevalence of diabetes mellitus and/or fasting blood sugar  $>100$  mg/100 ml in surviving co-twins according to cause of death of index-twin.

	IHD				not IHD			
	MZ No. %	DZ No. %	XZ No. %	Tot. No. %	MZ No. %	DZ No. %	XZ No. %	Tot. No. %
<b>Males:</b>								
A.	1 10.0	2 8.0	- 0.0	3 7.5	5 20.0	- 0.0	- 0.0	5 7.4
B.	1 10.0	4 16.0	- 0.0	5 12.5	5 20.0	2 4.8	- 0.0	7 10.3
Tot.	10	25	5	40	25	42	1	68
<b>Females:</b>								
A.	1 12.5	1 11.1	- 0.0	2 11.8	2 6.7	4 8.3	- 0.0	6 7.5
B.	2 25.0	1 11.1	- 0.0	3 17.6	3 10.0	4 8.3	- 0.0	7 8.8
Tot.	8	9	-	17	30	48	2	80

A=Diabetes mellitus; B=Diabetes mellitus and/or blood sugar  $>100$  mg/100

cases. The for what higher prevalence from other causes statistically in two of the concordant pairs. overt diabetes 187 mg/100 ml mellitus, having uria.

### Comments

In the present study, the fasting blood sugar was significantly higher in those whose partners died from IHD, and elevated fasting blood sugar. Neither did the presence of diabetes mellitus in pairs. However, diabetes mellitus has been reported by Sievers, 1963; and are of importance. The fact that 5 males with respect to diabetes mellitus also whether or not in the population (Gr

### URIC ACID

Clinical and epidemiological studies have shown that uric acid is more common in patients with diabetes mellitus. The possible mechanism is not clear. It is not clear if an increase in uric acid increases the risk of diabetes mellitus.

cases. The female co-twins whose partners died from IHD have somewhat higher prevalence rates than the co-twins whose partners died from other causes. None of the differences among the females is statistically significant. Diabetes mellitus was the cause of death in two of the deceased twins in the present material of death discordant pairs. One of their surviving co-twins (female DZ), also had overt diabetes treated with tablets. Her fasting blood sugar was 187 mg/100 ml. The other (male DZ) displayed no signs of diabetes mellitus, having a fasting blood sugar of 81 mg/100 ml and no glucosuria.

#### Comments

In the present investigation, overt diabetes mellitus and elevated fasting blood sugar do not appear to be responsible for the significantly higher prevalence of IHD manifestations among the male co-twins whose partners died from IHD compared to those whose partners did not die from IHD, because the prevalence of overt diabetes mellitus and elevated fasting blood sugar was about the same in both groups. Neither did the twin study by Liljefors (1970) indicate that the presence of diabetes mellitus is a determining factor for the occurrence of IHD in twins who probably had IHD in the IHD discordant pairs. However, in other studies an overrepresentation of diabetes mellitus has been reported among cases with IHD (Sievers et al, 1961; Sievers, 1963; Wahlberg, 1966; Simborg, 1970). That genetic factors are of importance for the occurrence of diabetes is underlined by the fact that 5 male MZ pairs (not IHD death discordant) were concordant with respect to overt diabetes mellitus. The prevalence of diabetes mellitus also seems rather high among the surviving co-twins, whether or not their partners died from IHD, compared to the general population (Grönberg et al, 1967; Bengtsson, 1973).

#### URIC ACID

Clinical and epidemiologic studies have shown that hyperuricaemia is more common in IHD subjects than in others (Gertler & White, 1954; Myers et al, 1968). Elevated uric acid has also been associated with an increased future risk of developing IHD (Kannel et al, 1967).

The possible etiologic role of uric acid in the development of IHD is not clear. Gertler & White (1964) suggested that uric acid could increase the adhesiveness of lipids to arterial walls. It has also

been proposed that uric acid influences thrombocyte aggregation (Newland, 1968). Studies by Theorell (1971) have shown that uric acid production is high in persons who have had myocardial infarction and that after the infarction the subjects do not regulate their renal excretion of uric acid as efficiently as do healthy subjects.

Twin studies have documented an influence of hereditary factors in the variation of uric acid levels (Harvald & Hauge, 1955; Jensen et al, 1965; Liljefors, 1970).

Material and Methods: see Chapters I and II.

### Results

The mean values for uric acid in the surviving co-twins with and without diuretic treatment are presented in Table 23. None of the differences between means among males and females respectively is statistically significant; this applies both to those with and to those without diuretics.

The distribution of co-twins with elevated uric acid ( $>6$  mg/100 ml) is given in Table 24, which includes those on diuretic therapy. Of the male co-twins whose partners died from IHD, 50 % have elevated uric acid compared to 29 % of those whose partners died from other causes. With the exception of one MZ co-twin whose partner had not died from IHD, all the male co-twins on diuretic therapy have elevated uric acid. Among the females the corresponding figures are 18 % compared to 10 %; out of 18 female co-twins on diuretic therapy, 5 have elevated uric acid (2 MZ with IHD partners and 3 DZ whose partners died from other causes). The differences in the occurrence of elevated uric acid are not statistically significant.

### Comments

As a larger proportion of the subjects whose partners had died from IHD were on diuretics, the analyses of the results are of course biased. When the co-twins on diuretic therapy are excluded, only slight differences are found among the others. The female MZ co-twins with partners who had died from IHD have higher uric acid levels on average than either the DZ twins in the same IHD group or the MZ twins whose partners had not died from IHD; to some extent this may be due to differences in weight as there is known to be a positive correlation between uric acid and obesity (Myers et al, 1968).

The differences in the occurrence of elevated uric acid are mainly due to the inclusion of persons receiving diuretic treatment, so that

Table 23. Distribution of means for uric acid in respondent co-twins with and without diuretic treatment according to cause of death of index-twin

Males						Females					
IHD			not IHD			IHD			not IHD		
MZ	DZ	XZ	Tot.	MZ	DZ	MZ	DZ	XZ	Tot.	MZ	DZ
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
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M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
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M	M	M	M	M	M	M	M	M	M	M	M
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M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
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M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
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M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
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M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
M	M	M	M	M	M	M	M	M	M	M	M
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M	M	M	M	M	M	M	M	M	M	M	M
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Table 23. Distribution of means for uric acid in respondent co-twins with and without diuretic treatment according to cause of death of index-twin

	Males								Females							
	IHD				not IHD				IHD				not IHD			
	MZ	DZ	XZ	Tot.	MZ	DZ	XZ	Tot.	MZ	DZ	XZ	Tot.	MZ	DZ	XZ	Tot.
	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)	(SE)
No diuretic therapy:																
Uric acid (mg/100 ml)	5.5 (0.2)	5.4 (0.3)	6.8 (0.7)	5.6 (0.2)	5.2 (0.3)	5.5 (0.2)	5.7 (0.0)	5.4 (0.1)	5.3 (0.3)	4.8 (0.2)	-	5.0 (0.2)	4.2 (0.2)	4.7 (0.2)	5.5 (0.0)	4.5 (0.1)
Number	7	23	5	35	23	42	1	66	5	7	-	12	24	42	1	67
Diuretic therapy:																
Uric acid (mg/100 ml)	6.4 (0.1)	6.9 (0.7)	-	6.6 (0.3)	4.6 (1.5)	-	-	4.6 (1.5)	7.4 (0.8)	4.8 (0.0)	-	6.3 (0.8)	4.8 (0.3)	6.0 (0.3)	6.0 (0.0)	5.5 (0.3)
Number	3	2	-	5	2	-	-	2	3	2	-	5	6	6	1	13

Elevated uric acid ( $\geq 6$ mg/100 ml)	IHD				not IHD			
	MZ No. (%)	DZ No. (%)	XZ No. (%)	Tot. No. (%)	MZ No. (%)	DZ No. (%)	XZ No. (%)	Tot. No. (%)
Males	5(50)	11(44)	4(80)	20(50)	8(32)	12(29)	0	20(29)
Tot.	10	25	5	40	25	42	1	68
Females	3(38)	0	-	3(18)	0	7(15)	1(50)	8(10)
Tot.	8	9	-	17	30	48	2	80

HEMOGLOBIN, HEMATOCRIT AND ERYTHROCYTE SEDIMENTATION RATE

Elevated hemoglobin values have been associated with an increased risk of IHD in men (Dawber & Kannel, 1961; Böttiger & Carlson, 1972). In a follow-up study of 50-year old men in Gothenburg (Tibblin, 1972), a high hematocrit level was associated with the incidence of both fatal and non-fatal myocardial infarction, but it also correlated with death from other causes than IHD, especially cancer. In the Stockholm Prospective Study, an elevated erythrocyte sedimentation rate (E.S.R.) has also been associated with an increased risk of IHD (Carlson & Böttiger, 1972).

Material and Methods: see Chapters I and II.

## Results

Table 25 gives the means for hemoglobin, hematocrit and erythrocyte sedimentation rate (E.S.R.). Both the male and the female values for hemoglobin and hematocrit are on average somewhat lower for the co-twins whose partners died from IHD than for those, whose partners died from other causes, although the differences are not statistically significant. With regard to E.S.R., the opposite applies. The differences between zygosity groups are also only slight and non-significant.

Table 25. Distribution of means for hemoglobin (Hb), hematocrit (Hct) and erythrocyte sedimentation rate (E.S.R.) in respondent co-twins according to cause of death of index-twin.

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Table 25. Distribution of means for hemoglobin (Hb), hematocrit (Hct) and erythrocyte sedimentation rate (E.S.R.) in respondent co-twins according to cause of death of index-twin.

	Males								Females							
	IHD				not IHD				IHD				not IHD			
	MZ M (SE)	DZ M (SE)	XZ M (SE)	Tot. M (SE)	MZ M (SE)	DZ M (SE)	XZ M (SE)	Tot. M (SE)	MZ M (SE)	DZ M (SE)	XZ M (SE)	Tot. M (SE)	MZ M (SE)	DZ M (SE)	XZ M (SE)	Tot. M (SE)
Hb (g/100 ml)	14.9 (0.4)	14.5 (0.3)	15.9 (0.3)	14.8 (0.2)	15.0 (0.3)	15.6 (0.3)	- <sup>1)</sup>	15.4 <sup>1)</sup> (0.2)	14.3 (0.4)	13.5 (0. )	-	13.8 (0.2)	14.0 (0.2)	13.9 <sup>1)</sup> (0.2)	8.8 (3.7)	13.8 <sup>1)</sup> (0.2)
Hct (%)	44.0 (1.0)	43.1 (0.9)	46.0 (0.9)	43.7 (0.6)	44.8 (0.8)	45.8 (0.7)	- <sup>1)</sup>	45.4 <sup>1)</sup> (0.5)	41.8 (0.9)	40.2 (0.9)	-	40.9 (0.7)	41.7 (0.6)	41.6 <sup>1)</sup> (0.7)	27.5 (12.5)	41.3 <sup>1)</sup> (0.6)
E.S.R. (mm/hour)	16.8 (5.8)	15.4 (2.9)	6.2 (1.2)	14.6 (2.3)	11.7 (1.9)	11.5 (1.7)	6.0 (0.0)	11.5 (1.3)	20.9 (5.8)	18.6 (3.4)	-	19.7 (3.2)	16.5 (2.4)	17.8 (2.2)	26.0 (2.0)	17.5 (1.6)
Total number	10	25	5	40	25	42	1	68	8	9	-	17	30	48	2	80

<sup>1)</sup>=Data missing from one subject.

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## Comments

As already mentioned, the Stockholm Prospective Study has identified high hemoglobin as a factor associated with an increased risk of IHD (Böttiger & Carlson, 1972). But the same study has also demonstrated a positive correlation, regardless of age, between the plasma lipids cholesterol and triglycerides, and hemoglobin (Böttiger & Carlson, 1973). Hemoglobin as a risk factor for IHD might thus be explained, not by the high hemoglobin value as such but by the concomitant increase in plasma lipids (Böttiger & Carlson, 1973). Furthermore, the Stockholm Prospective Study has established a positive correlation between elevated E.S.R. and cholesterol as well as triglycerides (Böttiger, 1973), while a recent study on asymptomatic hyperlipidaemic persons showed significantly elevated E.S.R. compared to normolipidaemic controls (Böttiger et al, 1973). The authors suggested that a possible reason for the raised E.S.R. could be that the hyperlipidaemia causes silent vascular disease (diagnosed as ST depressions during exercise), which in turn produces an elevated E.S.R.

## 3. ENVIRONMENT AMONG THE I

### SMOKING

The relationship between reports from the Surgeon General's association as well as a association in the above statistically between cigarette seems to be (Jenkins et al, 1965). pipe and cigarette (Fletcher & Rose, 1973). women than in men for women smokers.

Both acute and chronic effects of cigarette anoxemia when conceivable via nicotine via (Rose, 1973). between coronary (al, 1965). He consider that atherogenesis a sufficient study have shown duration of the Some epidemiological picture given up of nearly that smoking IHD in the U.S. Finland with a

### 3. ENVIRONMENTAL FACTORS ASSOCIATED WITH ISCHAEMIC HEART DISEASE AMONG THE DEATH DISCORDANT PAIRS

#### SMOKING

The relation of cigarette smoking to health has been reviewed in reports from the Royal College of Physicians in London (1971) and the Surgeon General of the U.S. Public Health Service (1972). A causal association probably exists between cigarette smoking and lung cancer as well as chronic obstructive lung disease. The question of a causal association with IHD has been much debated. From the studies reviewed in the above reports it is obvious that cigarette smoking is associated statistically with the excess male mortality from IHD. The connection between cigarette smoking and non-fatal myocardial infarction also seems to be strong but for angina pectoris it is more uncertain (Jenkins et al, 1968; Seltzer, 1968; Simborg, 1970). In most studies pipe and cigar smokers have not shown any increased risk of IHD (Fletcher & Horn, 1970). Although IHD death rates are much lower in women than in men, an increased mortality from IHD has been reported for women smokers, too (Hammond, 1966).

Both acute and chronic effects of smoking on the heart have been discussed. Among the acute effects, it has been proposed that the effects of carbon monoxide or nicotine may aggravate myocardial anoxemia when coronary artery flow is already reduced and it is conceivable that the risk of serious arrhythmias is enhanced by nicotine via the release of catecholamines (Fletcher & Horn, 1970; Rose, 1973). A chronic effect has been seen in the relationship between coronary atherosclerosis and cigarette smoking (Auerbach et al, 1965). However, Dawber & Kannel (1972) from the Framingham study consider that the cigarette habit, rather than tending to accelerate atherogenesis, triggers coronary attacks in persons predisposed by a sufficient degree of coronary atherosclerosis. The results of that study have shown that the risk of IHD is not associated with the duration of the habit but only with the daily intensity.

Some epidemiologic evidence conflicts, however, with the overall picture given by the major follow-up studies. The first 5 year follow-up of nearly 13,000 men in seven countries (Keys et al, 1970) showed that smoking was related to later myocardial infarction and death from IHD in the U.S.A. but not in the other countries, which included East Finland with the highest male IHD mortality in the world.